FUNCTIONALIZED (BENZOTRIAZOL-1-YL)METHANES AS 1,1-DIPOLE SYNTHON EQUIVALENTS IN ORGANIC SYNTHESIS

By

XIAOJING WANG

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To my parents, Mr. Zuoquan Wang, Mrs. Fangqin Kou, and my sister,
Ms. Xiaoling Wang, who always supported me

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Abstract of Dissertation Presented to the Graduate School
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FUNCTIONALIZED (BENZOTRIAZOL-1-YL)METHANES AS 1,1-DIPOLE SYNTHON EQUIVALENTS IN ORGANIC SYNTHESIS

By

Xiaojing Wang

August 2000

Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

Benzotriazole derived synthetic equivalents for 1,1-dipole synthons are easily accessible from inexpensive starting materials. Their use provides highly convenient, versatile and efficient routes to a great variety of valuable target compounds usually difficult to obtain by alternative methods and should be widely applicable in organic synthesis.

Chapter 2, Functionalized (benzotriazol-1-yl)methanes have been demonstrated to be useful as 1,1-dipole synthon equivalents in aromatic and heteroaromatic annulation reactions. Carbocyclic compounds like, dihydrophenanthrenes, tetrahydronaphthalene, indanes, tetrahydrochromanes and tetrahydroindoles with latent functionalities were thus prepared.

Chapter 3, Reactions of α-aryl-, α-heteroaryl- and α-heteroatom-substituted (benzotriazol-1-yl)methanes with chloro(trimethylsilyl)methane successfully provided intermediate 1-[2-(trimethylsilyl)ethylbenzotriazoles. Subsequent condensations with

aldehydes and ketones generated secondary allylic alcohols possessing aryl and heteroaryl substituents in the 2-position.

Chapter 4, 1-{1-[(Trimethylsilyl)methyl]prop-2-enyl}benzotriazole was applied successfully as a four-carbon unit for regiospecific syntheses of 2-alkyl-substituted 1,3-butadienes.

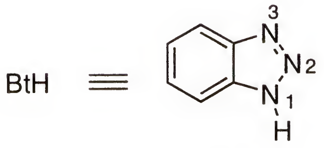
Chapter 5, Electron-rich 3-functionalized-2-aminothiophenes and 1,3-disubstituted-2-thiopyrroles were synthesized *via* annulation from substituted allyl benzotriazoles and isothiocyanates. Substituted allyl benzotriazoles were obtained in good yields.

Chapter 6, The readily deprotonation and subsequent reactions of easily available *N*-arylmethylene[(benzotriazole-1-yl)arylmethyl]amines with commercially available isothiocyanates were accomplished to generate *N*-substituted-2,4-diaryl-5-aminothiazoles in good yields.

CHAPTER 1
GENERAL INTRODUCTION

Our group commenced to investigate benzotriazole as a synthetic auxiliary in 1985. Since then, the unique properties of benzotriazole derivatives have been explored and used for the development of a variety of powerful synthetic methods [98CR409].

First of all, benzotriazole **1.1** (Figure 1.1*) is a stable, nontoxic and inexpensive compound. Its *N*-substituted derivatives are easily accessible in both large quantities and good yields [90JCS(P1)1847, 91RTC369, 94S597, 96JHC2031]. Moreover, benzotriazole derivatives are UV-active and hence can easily be traced; they are crystalline in many cases and they can usually be submitted to chromatography without decomposition. Therefore, reaction monitoring, work-up and purification are generally very convenient. All these facts provide a solid starting point for the development of benzotriazole chemistry.



1.1

Figure 1.1*

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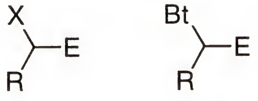
* Throughout all the schemes in the following chapters, Bt represents the 1-benzotriazolyl moiety.

Furthermore, the benzotriazolate anion is a good leaving group [89JCS(P1)225, 94JOC7209]. Therefore, halogen compounds such as **1.2** which are often physiologically dangerous and prone to hydrolysis can be replaced by their more stable and easy to handle benzotriazole analogues **1.3** (Figure 1.2).

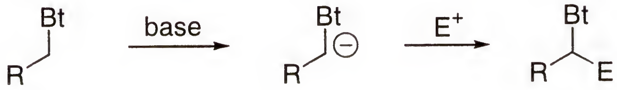


1.2 **1.3**

E: NR^1R^2 or OR^1
X: halogen

Figure 1.2

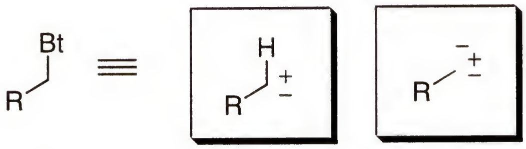
In addition, the benzotriazolyl moiety has excellent electron-acceptor properties. They are much better compared to those of, e.g. phenyl or vinyl groups. Therefore, most *N*-substituted benzotriazoles **1.4** possessing an α-proton can be deprotonated and the resulting carbanions **1.5** can be reacted with electrophiles (Scheme 1.1) [92LA843, 95JA12025, 97JA9321].



1.4 **1.5** **1.6**

Scheme 1.1

There is no doubt that the combination of all the advantageous properties of benzotriazole allows a wide spectrum of useful organic compounds in different kinds of organic reactions. It is thus the objective of this project to detail the investigations of functionalized (benzotriazol-1-yl)methanes **1.4** as 1,1-dipole synthon equivalents in organic synthesis (Figure 1.3). The results will be reported in following five chapters. As demonstrated, benzotriazole acts as not only an anion-stabilizing group, but also a good leaving group during reactions.



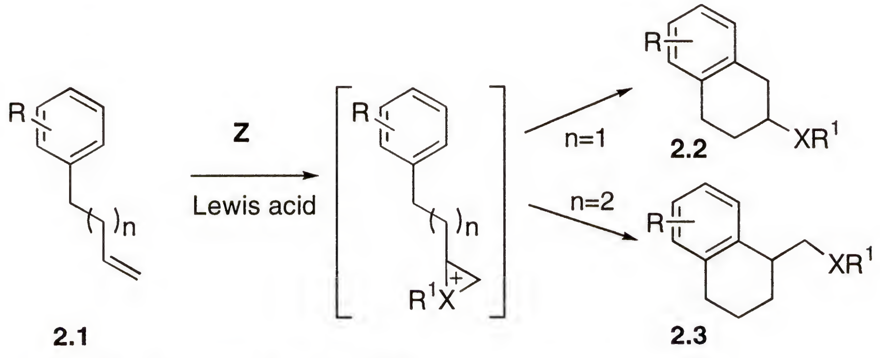
1.4

Figure 1.3

CHAPTER 2
FRIEDEL-CRAFTS TYPE REACTIONS: DIVERSE ANNULATIONS TO AROMATIC AND HETEROAROMATIC RINGS

2.1 Introduction

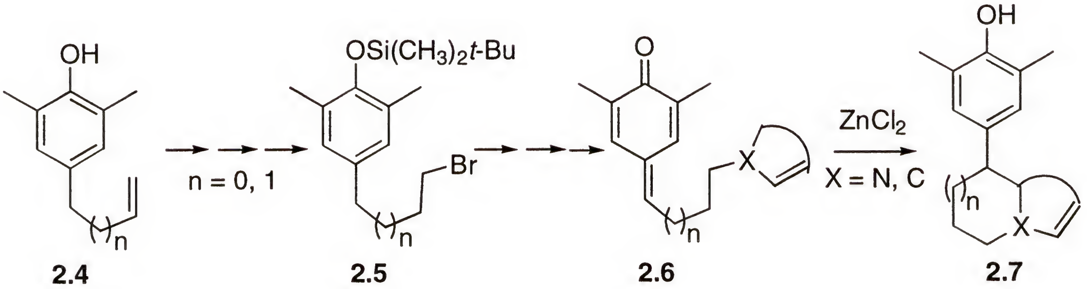
Aromatic annulations forming carbocyclic derivatives bearing latent functionality are of importance for natural product synthesis [97TL2397, 97TL6087, 98SL365, 89JA5472, 91CR5]. However, so far the types of latent functionality introduced by such annulations are quite limited. There are, e.g., arene-alkene carboannulations initiated by both episelenonium ions and episulfonium ions (Scheme 2.1) [86JA1334, 86TL3483]. However, annulations on non-activated aromatic compounds only provided low yields. In addition, these methodologies were limited to the formation of six-membered rings.



a. **Z** = $PhSOCH_3$ ($R^1X = PhS$);
b. **Z** = *N*-(phenylseleno)succinimide ($R^1X = PhSe$).

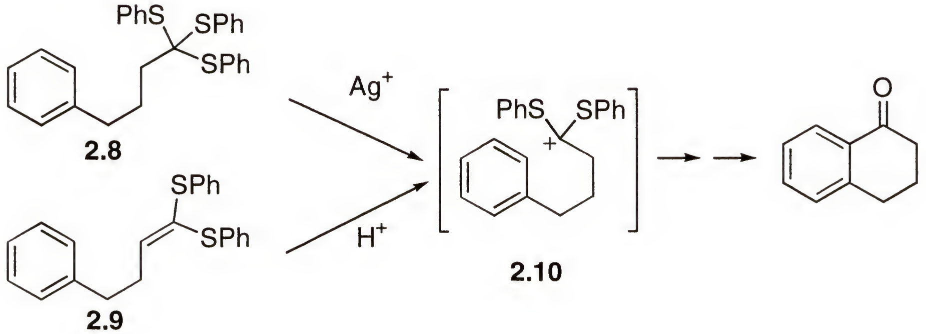
Scheme 2.1

Quinone methides **2.6** generated by Ag_2O oxidation of *p*-substituted phenols were also used to initiate intramolecular cyclization [89TL1193]. However, the substituent on the newly formed aliphatic ring was limited to only the 4-hydroxy-3,5-dimethylphenyl group.



Scheme 2.2

Further examples are intramolecular aromatic electrophilic substitutions initiated by dithiin carbocations **2.10** generated *in situ* by treatment of **2.8** with a silver salt or by protonation of **2.9** [90T2111, 90JOC5078] as shown in Scheme 2.3. However, this method is also limited to the formation of six-membered rings and requires the use of highly toxic HgO [95MI3257] for the removal of thiophenolate auxiliary.



Scheme 2.3

Earlier work from our laboratory revealed that (1-phenylthiomethyl)benzotriazole ($BtCH_2SPh$) to be a valuable annulating reagent for the synthesis of phenylthio-substituted carbocyclic compounds [93H1367]. It is thus our intention to extend the scope of this methodology to a wide range of functionalized (benzotriazol-1-yl)methanes

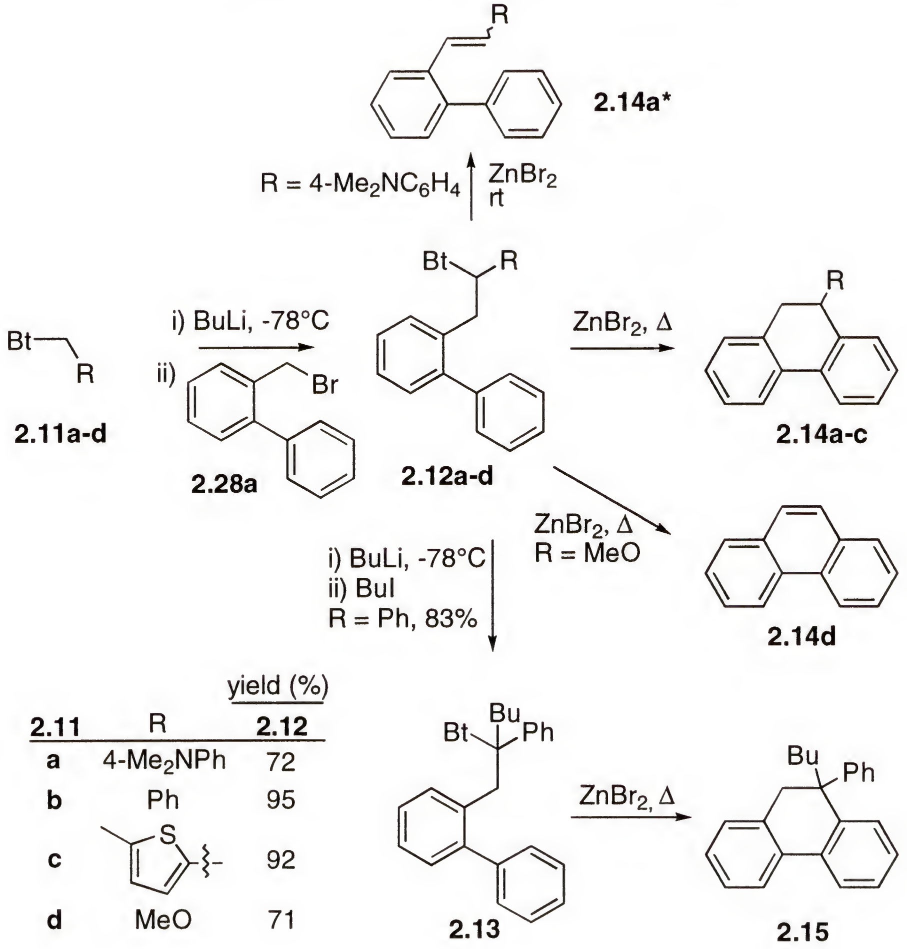
($BtCH_2R$) and to use them as 1,1-dipole synthetic equivalents in reactions with aromatic and heteroaromatic compounds.

2.2 Results and Discussion

1-[4-(*N,N*-Dimethylamino)benzyl]benzotriazole (**2.11a**) [90S341], 1-benzylbenzotriazole (**2.11b**) [85H2895], 5-methyl-2-(benzotriazol-1-ylmethyl)thiophene (**2.11c**) [96JOC7571], 1-(methoxymethyl)benzotriazole (**2.11d**) [87JCS(P1)791], and 1-(4-methylbenzyl)benzotriazole (**2.11e**) [56JCS1076], were synthesized in multi-gram-scale according to previously reported procedures.

Treatment of **2.11a-d** with BuLi at –78 °C under argon, followed by the addition of 2-(bromomethyl)biphenyl (**2.28a**), gave the compounds **2.12a-d** in excellent yields. It was possible as well to obtain the disubstituted product **2.13** in 83% yield simply by deprotonation of **2.12b** and subsequent alkylation of the resulting carbanion with *n*-BuI using analogous reaction conditions.

A preliminary attempt to achieve intramolecular alkylation monitored with TLC was performed by stirring compound **2.12a** in methylene chloride with $ZnBr_2$ at room temperature for 2 h. The complete consumption of starting material **2.12a**, the appearance of BtH and another product were observed. However, the new product was not the expected phenanthrene **2.14a** but the olefin **2.14a*** resulting from the elimination of benzotriazole (Scheme 2.4). We reasoned that at higher temperature, olefins could be cyclized to the desired products under the same condition without being isolated. Indeed compound **2.14a** was obtained by raising the reaction temperature to 130 °C in 61% yield. The 9-monosubstituted dihydrophenanthrenes **2.14b** and **2.14c** were formed similarly in even better yields (Table 2.1). However, an attempt to perform the annulation with **2.12d** under similar conditions only provided phenanthrene **2.14d** in 81% yield, due to presumably annulation and subsequent elimination of methanol. We also applied our method successfully for the synthesis of the 9,9-disubstituted dihydrophenanthrene **2.15** by the cyclization of compound **2.13**.



2.11	R	yield (%) 2.12
a	4-Me$_2$NPh	72
b	Ph	95
c		92
d	MeO	71

Scheme 2.4

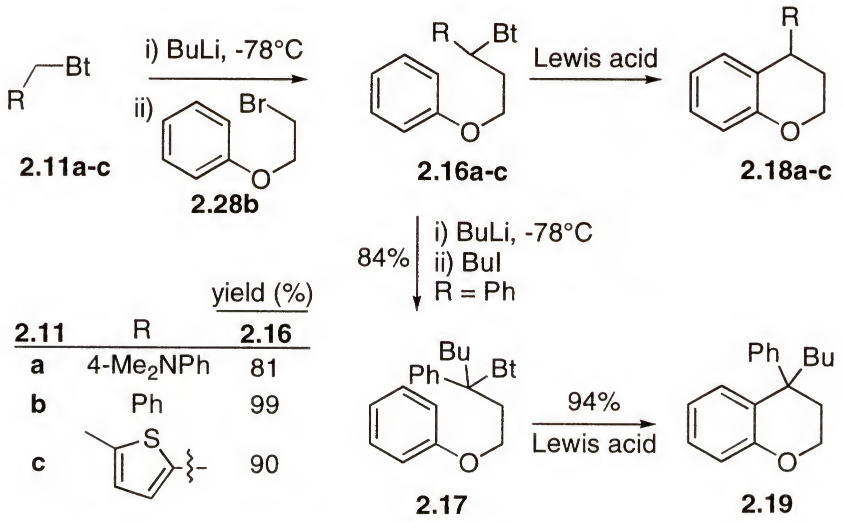
Following the procedure described above, but using 2-phenoxy-1-bromoethane (**2.28b**) instead of **2.28a**, the benzotriazole derivatives **2.16a-c** and subsequently **2.17** were obtained. These were successfully transformed to the annulated monosubstituted compounds **2.18a-c** or the disubstituted compound **2.19**, respectively (Scheme 2.5, Table

2.1). The low yield of **2.18a** is perhaps caused by the formation of polymers. This hypothesis is supported by the observation of the total consumption of the starting material **2.16a** and the appearance of unidentified colorful by-products.

Table 2.1. Reaction Conditions for the Synthesis of Annulated Compounds.

Compd.	Lewis acid	Reaction time	temperature	solvent	yield
2.14a	$ZnBr_2$ (2.0)	24	130	1,2-dichlorobenzene	61
2.14b	$AlCl_3$ (1.0)	72	120	1,2-dichlorobenzene	85
2.14c	$ZnBr_2$ (2.0)	22	25	chloroform	95
2.14d	$ZnBr_2$ (2.0)	5	62	chloroform	81
2.15	$ZnBr_2$ (2.0)	0.5	105	1,2-dichlorobenzene	97
2.18a	$ZnBr_2$ (2.0)	29	40	methylene chloride	20
2.18b	$ZnBr_2$ (1.0)	24	170	1,2-dichlorobenzene	70
2.18c	$ZnBr_2$ (1.0)	12	120	1,2-dichlorobenzene	76
2.19	$ZnBr_2$ (1.0)	5	115	1,2-dichlorobenzene	94
2.22c	$ZnBr_2$ (2.0)	24	62	chloroform	49
2.22e	$ZnBr_2$ (1.8)	12 (24)[a]	130 (160)[a]	1,2-dichlorobenzene	49
2.23	$ZnBr_2$ (2.0)	12 (24)[a]	140 (160)[a]	1,2-dichlorobenzene	61
2.26	$ZnBr_2$ (1.3)	1	150	1,2-dichlorobenzene	57
2.27	$ZnBr_2$ (1.0)	12	120	1,2-dichlorobenzene	97

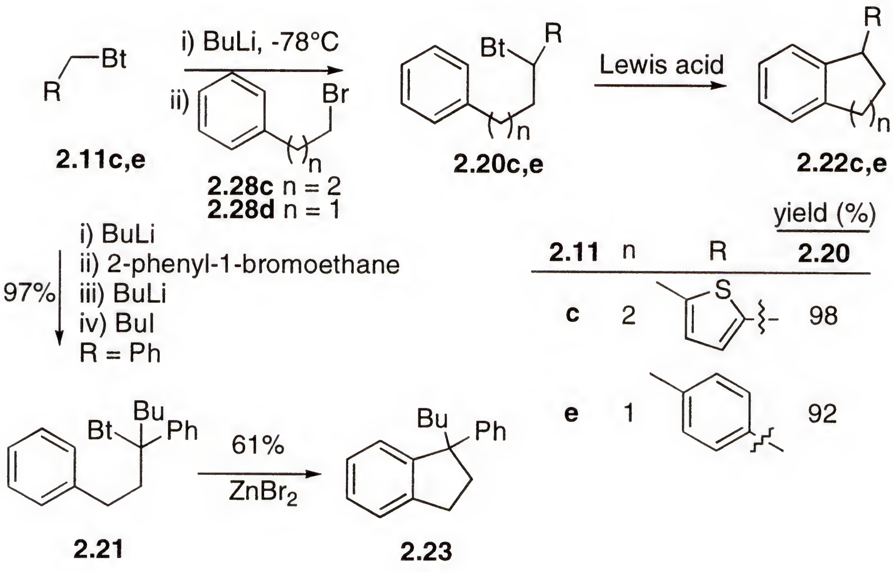
[a] The reaction mixture was heated in two stages for the time and at the temperature indicated.



Scheme 2.5

Furthermore, the benzotriazole derivatives **2.20c**, **2.20e**, and **2.21** were obtained in good yields (Scheme 2.6). These were transformed successfully to the desired 1-substituted tetrahydronaphthalene **2.22c**, the 1-substituted indane **2.22e**, and 1,1-disubstituted indane **2.23**, albeit in moderate yields (Table 2.1). Especially, the annulation of **2.20e** proved to be difficult and significant amounts of the corresponding (E)- and (Z)-olefins resulting from the elimination of benzotriazole were formed as indicated by ^{1}H NMR and GC-MS spectra of the crude product. However, the cyclization of compound **2.20e** in a reasonable yield was finally accomplished by increasing the reaction temperature and the reaction time (Table 2.1).

In summary, our results (Table 2.1) indicate that electron-rich R groups α to Bt moiety facilitated the ring formation, because in these cases the annulation usually took place under milder reaction conditions providing the desired products in higher yields.

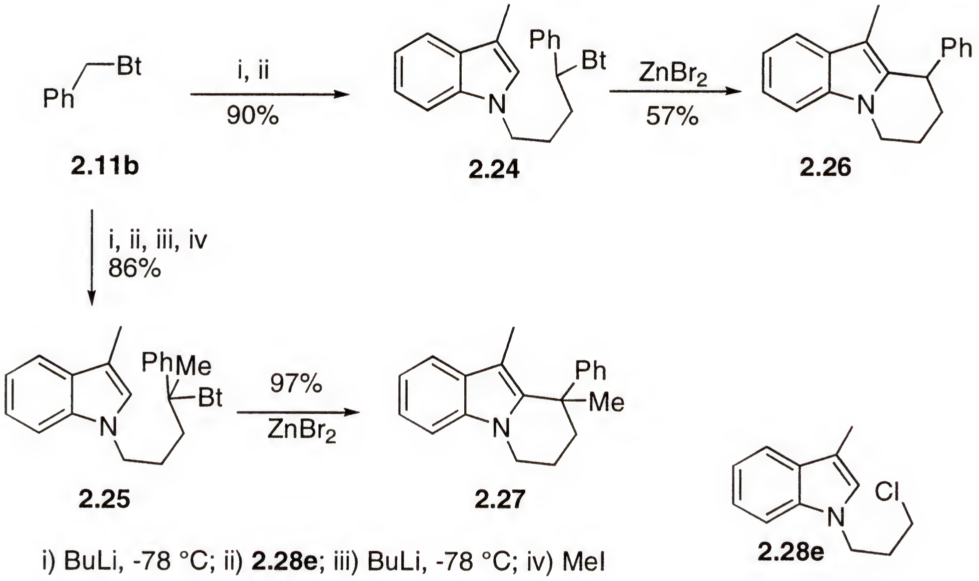


Scheme 2.6

Due to the pharmacological activities of mitomycins [79MI1, 83MI2, 93CPB854], the search for new drugs by the modification of the mitomycin skeleton and the mitomycin-like 1,2,3,4-tetrahydropyrido[1,2-*a*]indoles has attracted much attention.

Existing methods for the construction of the 1,2,3,4-tetrahydropyrido[1,2-*a*]indoles skeleton include (i) intramolecular radical cyclizations [93SL231, 96JCS(P1)675, 94JOC2456, 95TL4857], (ii) a Dieckmann/ring expansion approach [91T4645], and (iii) our benzotriazole-mediated annulation method *via* 1-(1*H*-2-indolylmethyl)-1*H*-benzotriazole [97JOC4148]. We have found that this methodology can be further extended to provide a straightforward alternative route to 1-substituted 1,2,3,4-tetrahydropyrido[1,2-*a*]indoles.

The starting material **2.28e** was easily synthesized according to a literature procedure [90H447]. It was used successfully for the preparation of the cyclization precursors **2.24** and **2.25** in 90% and 86% yield, respectively (Scheme 2.7). The annulation of compound **2.24** afforded **2.26** in 57% yield. However, a preliminary experiment indicated that **2.26** was prone to decomposition under the reaction conditions used. Hence, the reaction should be monitored by TLC and the reaction mixture should be worked up as soon as possible in order to achieve an optimum yield. On the other hand, compound **2.27** was obtained in an excellent yield (Scheme 2.7), presumably because of its greater stability compared to **2.26** and due to the fact that a stabilized tertiary carbocation is formed in the course of the reaction.



i) BuLi, -78 °C; ii) **2.28e**; iii) BuLi, -78 °C; iv) MeI

Scheme 2.7

2.3 Experimental Section

Melting points were determined with a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or $CDCl_3$ as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. Column chromatography was conducted with silica gel (230–400 mesh) or neutral alumina (60–325 mesh), Brockman activity I. Column chromatographic separations were performed, unless otherwise stated, with hexanes and 0.0, 0.5, 1.0, 2.5, 5.0, 7.5, and 10.0% v/v diethyl ether gradient and a flow rate of 20–30 mL/min.

2.3.1 General Procedure for the Synthesis of Intermediates 2.12a-d, 2.13, 2.16a-c, 2.17, 2.20c, 2.20e, 2.21, 2.24, and 2.25.

To a solution of the appropriate **2.11a-d** (1 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi in hexane (1.6 M, 1.1 mmol). After 10 min, a solution of the appropriate alkyl halide **2.28a-e** (1 mmol) dissolved in THF (5 mL) was added. The mixture was stirred at −78 °C for 3 h and then allowed to warm to rt overnight. For the synthesis of **2.13**, **2.17**, **2.21**, and **2.25**, the mixture was cooled to −78 °C and *n*-BuLi in hexane (1.6 M, 1 mmol) was added. After 5 min, *n*-butyl iodide (in the case of **2.13**, **2.17**, and **2.21**) or methyl iodide (in the case of **2.25**) (1 mmol) was added. After 3 h at −78 °C, the mixture was allowed to warm to rt overnight. The solvent was evaporated under reduced pressure, and the residue was treated with water (10 mL) and ethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$). The crude product was purified as described below.

2-[2-(1*H*-Benzotriazol-1-yl)-2-(4-*N,N*-dimethylaminophenyl)ethyl]biphenyl (**2.12a**): Recrystallized from ethyl ether, gray powder, mp 145.0–146.1 °C; ^{1}H NMR δ 2.84 (s, 6H), 3.83 (dd, *J* = 6.0, 14.2 Hz, 1H), 4.05 (dd, *J* = 9.6, 13.5 Hz, 1H), 5.59 (t, *J* = 8.8 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 7.00–7.54 (m, 12H), 7.94 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR δ 39.2, 40.3, 63.1, 109.6, 112.1, 119.6, 123.4, 126.4, 126.6, 126.7, 127.1, 127.3, 127.4, 128.4, 129.1, 130.0, 130.7, 132.8, 134.7, 141.5, 142.0, 145.8, 150.1. Anal. Calcd for $C_{28}H_{26}N_4$: C, 80.34; H, 6.27; N, 13.39. Found: C, 80.12; H, 6.51; N, 13.49.

2-[2-(1*H*-Benzotriazol-1-yl)-2-phenylethyl]biphenyl (**2.12b**): Separated by gradient column chromatography on silica gel, colorless oil; ^{1}H NMR δ 3.86 (dd, *J* = 6.3, 14.4 Hz, 1H), 4.09 (dd, *J* = 9.3, 14.1 Hz, 1H), 5.61 (dd, *J* = 6.0, 9.3 Hz, 1H), 6.89–7.49 (m, 17H), 7.96 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR δ 39.8, 63.8, 109.8, 120.2, 124.1, 126.9, 127.3, 127.3, 127.7, 127.8, 128.4, 129.0, 129.5, 130.5, 131.2, 133.4, 134.7, 139.3, 141.8, 142.5, 146.2. Anal. Calcd for $C_{26}H_{21}N_3$: C, 83.17; H, 5.64; N, 11.19. Found: C, 83.34; H, 5.50; N, 10.80.

2-[2-(1*H*-Benzotriazol-1-yl)-2-(5-methyl-2-thienyl)ethyl]biphenyl (2.12c): White needles, mp 107.8–108.5 °C (hexanes/ethyl acetate, 1:15); ^{1}H NMR δ 2.32 (s, 3H), 3.89–3.96 (m, 2H), 5.88 (dd, *J* = 6.6, 8.8 Hz, 1H), 6.44 (d, *J* = 3.4 Hz, 1H), 6.49 (d, *J* = 2.6 Hz, 1H), 7.00–7.06 (m, 3H), 7.12–7.17 (m, 2H), 7.24–7.29 (m, 4H), 7.38–7.43 (m, 3H), 7.96 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR δ 15.1, 39.8, 59.2, 109.5, 119.8, 123.6, 124.6, 125.5, 126.9, 127.0, 127.2, 127.4, 128.5, 129.0, 130.1, 130.4, 132.4, 133.8, 138.9, 140.3, 141.2, 142.0, 145.9. Anal. Calcd for $C_{25}H_{21}N_3S$: C, 75.92; H, 5.35; N, 10.62. Found: C, 75.77; H, 5.38; N, 10.65.

2-[2-(1*H*-Benzotriazol-1-yl)-2-methoxyethyl]biphenyl (2.12d): Oil separated by gradient column chromatography on silica gel, light yellow; ^{1}H NMR δ 3.09 (s, 3H), 3.43 (dd, *J* = 6.9, 14.1 Hz, 1H), 3.63 (dd, *J* = 6.6, 14.1 Hz, 1H), 5.94 (t, *J* = 6.9 Hz, 1H), 7.15–7.34 (m, 12H), 7.99–8.02 (m, 1H); ^{13}C NMR δ 38.0, 56.6, 92.2, 110.8, 119.9, 124.0, 127.0, 127.1, 127.3, 127.5, 128.2, 129.1, 130.0, 130.2, 131.3, 132.5, 141.0, 142.6, 146.5. Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.37; H, 5.79; N, 12.57.

2-[2-(1*H*-Benzotriazol-1-yl)-2-*n*-butyl-2-phenylethyl]biphenyl (2.13): Separated by gradient column chromatography on alumina, colorless solid, mp 66.3–69.0 °C; ^{1}H NMR δ -0.01–0.04 (m, 1H), 0.55 (t, *J* = 7.1 Hz, 3H), 0.55–0.67 (m, 1H, overlapped), 0.89–1.04 (m, 2H), 2.12–2.32 (m, 2H), 4.20 (d, *J* = 13.5 Hz, 1H), 4.38 (d, *J* = 13.8 Hz, 1H), 6.09 (d, *J* = 7.7 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 7.3 Hz, 2H), 6.87–6.91 (m, 1H, overlapped), 7.04–7.38 (m, 12H), 8.06 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 13.5, 22.5, 25.2, 36.6, 38.5, 71.4, 112.3, 119.7, 123.3, 126.1, 126.3, 126.5, 126.6, 126.7, 127.5, 128.1, 128.2, 129.4, 130.5, 131.0, 132.3, 132.5, 141.5, 142.0, 143.5, 146.6.

Anal. Calcd for $C_{30}H_{29}N_3O$: C, 83.49; H, 6.77; N, 9.74. Found: C, 83.29; H, 6.97; N, 9.66.

***N*-{4-[1-(1*H*-Benzotriazol-1-yl)-3-phenoxypropyl]phenyl}-*N,N*-dimethyl-amine** (**2.16a**): White microcrystals; mp 106.1–107.2 °C (hexanes/ethyl acetate, 10:1); ^{1}H NMR δ 2.89 (s, 6H), 2.89–2.97 (m, 1H, overlapped), 3.18–3.27 (m, 1H), 3.96 (t, *J* = 5.6 Hz, 2H), 6.08 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 7.21–7.36 (m, 5H), 7.42 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 34.8, 40.3, 59.6, 64.0, 110.0, 112.3, 114.5, 119.7, 120.8, 123.7, 125.9, 126.9, 127.8, 129.4, 132.9, 146.1, 150.3, 158.5. Anal. Calcd for $C_{23}H_{24}N_4O$: C, 74.17; H, 6.49; N, 15.04. Found: C, 74.23; H, 6.35; N, 15.11.

1-(3-Phenoxy-1-phenylpropyl)-1*H*-benzotriazole (**2.16b**): Separated by gradient column chromatography on silica gel, light yellow oil; ^{1}H NMR δ 2.91–2.96 (m, 1H), 3.26–3.30 (m, 1H), 3.94–3.99 (m, 2H), 6.16 (dd, *J* = 6.6, 8.7 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 7.21–7.41 (m, 10H), 8.04 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 35.0, 59.8, 63.9, 109.7, 114.5, 119.9, 121.0, 123.9, 126.8, 127.2, 128.4, 128.9, 129.4, 133.1, 138.8, 146.1, 158.4. Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.61; H, 6.10; N, 13.10.

1-[3-Phenoxy-1-(5-methylthiophen-2-yl)propyl]-1*H*-benzotriazole (**2.16c**): Separated by gradient column chromatography on silica gel, light yellow oil; ^{1}H NMR δ 2.38 (s, 3H), 2.95–3.02 (m, 1H), 3.13–3.19 (m, 1H), 3.82–3.89 (m, 1H), 3.96–4.03 (m, 1H), 6.42 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 2.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.89–6.93 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 15.2, 35.3, 55.6, 63.7, 109.8, 114.5, 120.0, 121.0, 123.9, 124.8, 126.1, 127.2, 129.4, 132.5, 138.8, 140.7, 146.1, 158.3. Anal. Calcd for $C_{20}H_{19}N_3OS$: C, 68.74; H, 5.48; N, 12.02. Found: C, 68.81; H, 5.54; N, 12.39.

1-(1-Butyl-3-phenoxy-1-phenylpropyl)-1*H*-benzotriazole (**2.17**): Separated by gradient column chromatography on alumina, white solid; mp 105.7–107.7 °C; ^{1}H NMR δ 0.79 (t, *J* = 6.9 Hz, 3H), 0.70–0.90 (m, 1H, overlapped), 1.12–1.39 (m, 3H), 2.63–2.83 (m, 2H), 3.08–3.26 (m, 2H), 3.54–3.62 (dd, *J* = 6.9, 16.5 Hz, 1H), 3.97–4.05 (m, 1H), 6.66 (t, *J* = 8.3 Hz, 3H), 6.88 (t, *J* = 7.4 Hz, 1H), 7.10–7.37 (m, 9H), 8.06 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 13.8, 22.7, 25.4, 36.2, 37.5, 63.2, 69.4, 112.1, 114.2, 120.0, 120.7, 123.6, 126.3, 126.5, 128.0, 128.8, 129.3, 132.1, 142.1, 146.9, 158.3. Anal. Calcd for $C_{25}H_{27}N_3O$: C, 77.89; H, 7.06; N, 10.90. Found: C, 78.17; H, 7.37; N, 11.21.

1-[1-(5-Methyl-2-thienyl)-4-phenylbutyl]-1*H*-benzotriazole (**2.20c**): Recrystallized from hexanes/ethyl acetate, 1:30, light yellow powder; mp 99.2–100.3 °C; ^{1}H NMR δ 1.47–1.71 (m, 2H), 2.34 (s, 3H), 2.45–2.74 (m, 4H), 6.07 (dd, *J* = 6.3, 9.0 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 3.3 Hz, 1H), 7.06–7.42 (m, 8H), 8.03 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 15.1, 27.9, 34.4, 34.9, 59.2, 109.9, 119.9, 123.7, 124.6, 125.6, 125.8, 127.0, 128.1, 128.2, 132.0, 139.2, 140.3, 141.2, 146.2. Anal. Calcd for $C_{21}H_{21}N_3S$: C, 72.59; H, 6.09; N, 12.09. Found: C, 72.29; H, 6.43; N, 12.09.

1-[1-(4-Methylphenyl)-3-phenylpropyl]-1*H*-benzotriazole (**2.20e**): Separated by column chromatography on silica gel with hexanes/ethyl acetate, 4:1, colorless oil; ^{1}H NMR δ 2.29 (s, 3H), 2.58–2.82 (m, 3H), 3.11–3.24 (m, 1H), 5.72 (dd, *J* = 6.0, 9.6 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 2H), 7.18–7.39 (m, 10H), 8.07 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 21.0, 32.4, 36.2, 62.3, 109.8, 119.9, 123.8, 126.2, 126.7, 127.0, 128.5, 129.5, 132.8, 136.1, 138.0, 140.4, 146.2. Anal. Calcd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.48; N, 12.84. Found: C, 80.50; H, 6.47; N, 13.04.

3-(1,3-Diphenylheptyl)-1*H*-benzotriazole (**2.21**): Separated by column chromatography on silica gel with hexanes/ethyl acetate, 4:1, yellow oil; ^{1}H NMR δ 0.82 (t, *J* = 7.6 Hz, 3H), 0.80–0.84 (m, 1H, overlapped), 1.18–1.32 (m, 3H), 1.98–2.08 (m, 1H), 2.52–2.69 (m, 2H), 2.79–3.02 (m, 3H), 6.69 (d, *J* = 8.3 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 2H), 7.08–7.34 (m, 10H), 8.08 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 13.8, 22.7, 25.3, 29.8 36.9, 38.9, 70.2, 112.1, 119.9, 123.5, 125.9, 126.3, 127.8, 128.2, 128.3, 128.6, 132.2, 141.1, 142.4, 146.8. Anal. Calcd for $C_{25}H_{27}N_3$: C, 81.26; H, 7.38; N, 11.37. Found: C, 81.03; H, 7.57; N, 11.16.

1-[4-(3-Methyl-1*H*-indol-1-yl)-1-phenylbutyl]-1*H*-benzotriazole (**2.24**): Separated by gradient column chromatography on silica gel, light yellow microcrystals, mp 120.9–122.2 °C; ^{1}H NMR δ 1.70–1.75 (m, 2H), 2.25 (s, 3H), 2.31–2.40 (m, 1H), 2.72–2.79 (m, 1H), 3.96 (t, *J* = 6.8 Hz, 2H), 5.36 (dd, *J* = 6.3, 8.9 Hz, 1H), 6.69 (s, 1H), 7.00–7.24 (m, 11H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H);^{13}C NMR δ 9.8, 27.2, 32.7, 45.7, 63.2, 109.3, 109.9, 110.6, 118.9, 119.3, 120.0, 121.8, 124.1, 125.5, 126.9, 127.3, 128.5, 129.0, 133.0, 136.4, 139.1, 146.3. Anal. Calcd for $C_{25}H_{24}N_4$: C, 78.92; H, 6.36; N, 14.73. Found: C, 78.85; H, 6.53; N, 14.49.

1-[1-Methyl-4-(3-methyl-1*H*-indol-1-yl)-1-phenylbutyl]-1*H*-benzotriazole (**2.25**): Separated by gradient column chromatography, light yellow oil; ^{1}H NMR δ 1.35–1.41 (m, 1H), 1.71–1.77 (m, 1H), 1.94 (s, 3H), 2.16 (s, 3H), 2.41–2.51 (m, 1H), 2.56–2.66 (m, 1H), 3.80–3.89 (m, 2H), 6.46 (d, *J* = 8.5 Hz, 1H), 6.56 (s, 1H), 6.91–7.03 (m, 6H), 7.06–7.16 (m, 4H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 9.5, 24.7, 26.7, 37.9, 45.6, 67.2, 108.9, 110.2, 111.9, 118.4, 118.9, 119.8, 121.3, 123.5, 124.9, 125.6, 126.5, 127.8, 128.6, 128.7, 132.0, 136.1, 142.9, 146.8. Anal. Calcd for $C_{26}H_{26}N_4$: C, 79.16; H, 6.64; N, 14.20. Found: C, 79.22; H, 6.94; N, 14.24.

2.3.2 General Procedure for the Synthesis of Compounds 2.14a-d, 2.15, 2.18a-c, 2.19, 2.22c, 2.22e, 2.23, 2.26, and 2.27.

To a solution of **2.12a-d, 2.13, 2.16a-c, 2.17, 2.20c, 2.20e, 2.21, 2.24, or 2.25** (1 mmol) in the appropriate solvent (Table 2.1) (50 mL) was added the appropriate Lewis acid (for the type and amount see Table 2.1). The mixture was stirred at the temperature indicated (Table 2.1) until the intermediates were consumed (indicated in Table 2.1). The solvent was removed under reduced pressure, and the residue was treated with dichloromethane (10 mL) and aqueous sodium hydroxide solution (2 M, 25 mL). The aqueous layer was extracted with dichloromethane (3 × 15 mL) and dried ($MgSO_4$). The crude product was purified as described below.

9-(4-*N,N*-Dimethylaminophenyl)-9,10-dihydrophenanthrene (2.14a): Separated by column chromatography on silica gel with hexanes/ethyl acetate, 10:1, colorless oil; ^{1}H NMR δ 2.88 (s, 6H), 3.09–3.22 (m, 2H), 4.08 (dd, *J* = 5.8, 9.1 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 7.13–7.21 (m, 3H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.78 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR δ 37.1, 40.6, 43.8, 112.7, 123.5, 123.6, 126.9, 127.0, 127.5, 128.3, 128.4, 129.0, 131.2, 134.4, 136.3, 140.7, 149.3. Anal. Calcd for $C_{22}H_{21}N$: C, 88.24; H, 7.08; N, 4.68. Found: C, 88.13; H, 7.41; N, 4.72.

9-Phenyl-9,10-dihydrophenanthrene (2.14b): Separated by column chromatography on silica gel with hexanes as solvent, white solid, mp 72.4–74.4 °C (lit. [37JA1443] mp 84 °C); ^{1}H NMR δ 3.15–3.21 (m, 2H), 4.19 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 7.09–7.35 (m, 10H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H); ^{13}C

NMR δ 37.1, 44.8, 123.6, 123.8, 126.5, 127.1, 127.2, 127.6, 128.3, 128.4, 134.4, 134.5, 135.8, 139.8, 143.4. Anal. Calcd for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.47; H, 6.57.

9-(5-Methyl-2-thienyl)-9,10-dihydrophenanthrene (**2.14c**): Separated by column chromatography on silica gel with hexanes as solvent, light yellow oil; ^{1}H NMR δ 2.30 (s, 3H), 3.14 (dd, *J* = 7.2, 15.0 Hz, 1H), 3.24 (dd, *J* = 5.4, 15.0 Hz, 1H), 4.33 (dd, *J* = 5.4, 7.2 Hz, 1H), 6.43 (s, 2H), 7.13–7.31 (m, 6H), 7.73 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR δ 15.2, 37.1, 40.1, 123.5, 123.8, 124.3, 124.7, 127.2, 127.5, 127.6, 128.1, 128.7, 133.7, 134.0, 135.1, 138.0, 139.3, 144.4. Anal. Calcd for $C_{19}H_{16}S$: C, 82.56; H, 5.83. Found: C, 82.87; H, 6.10.

Phenanthrene (**2.14d**): Separated by column chromatography on silica gel with hexanes as solvent; white microcrystals, mp 99.1–100.5 °C (lit. [90H447] mp 101 °C); ^{1}H NMR δ 7.56–7.67 (m, 4H), 7.73 (s, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 8.68 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 123.1, 127.0, 127.3, 129.0, 130.7, 132.5.

9-*n*-Butyl-9-phenyl-9,10-dihydrophenathrene (**2.15**): Separated by column chromatography on alumina with hexanes as solvent, colorless oil; ^{1}H NMR δ 0.83 (t, *J* = 7.1 Hz, 3H), 1.13–1.46 (m, 4H), 1.94–2.00 (m, 2H), 3.04 (d, *J* = 15.4 Hz, 1H), 3.43 (d, *J* = 15.4 Hz, 1H), 7.07–7.34 (m, 11H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.79 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 14.0, 23.3, 27.3, 38.5, 40.9, 46.3, 123.4, 124.3, 125.7, 126.8, 127.2, 127.5, 127.8, 128.4, 134.1, 134.4, 135.7, 142.9, 146.4. Anal. Calcd for $C_{24}H_{24}$: C, 92.26; H, 7.74. Found: C, 92.16; H, 7.89.

***N,N*-Dimethyl-4-(3,4-dihydro-2*H*-4-chromenyl)aniline** (**2.18a**): Separated by column chromatography on silica gel with hexanes as solvent, light yellow microcrystals; mp 50.8–51.1 °C; ^{1}H NMR δ 1.94–2.10 (m, 1H), 2.13–2.27 (m, 1H), 2.86 (s, 6H), 4.02 (t, *J* = 6.3 Hz, 1H), 4.10–4.13 (m, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 6.67–6.82 (m, 3H), 6.93

(d, *J* = 8.4 Hz, 2H), 7.04 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR δ 31.8, 40.1, 40.7, 64.0, 112.6, 116.6, 120.2, 127.2, 127.5, 129.2, 130.7, 133.5, 149.3, 155.1. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.93; H, 7.88; N, 5.22.

4-Phenylchromane (**2.18b**): Separated by column chromatography on alumina with hexanes as solvent, light yellow oil (lit. [72BSF1540] mp 44 °C); ^{1}H NMR δ 2.02–2.13 (m, 1H), 2.24–2.32 (m, 1H), 4.10–4.18 (m, 3H), 6.75–6.88 (m, 3H), 7.09–7.31 (m, 6H); ^{13}C NMR δ 31.6, 41.0, 63.8, 116.7, 120.3, 124.5, 126.4, 127.8, 128.4, 128.6, 130.6, 145.6, 155.1. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.79; H, 6.91.

4-(5-Methylthiophen-2-yl)chromane (**2.18c**): Separated by column chromatography on alumina with hexanes as solvent, light yellow oil; ^{1}H NMR δ 2.08–2.18 (m, 1H), 2.25–2.40 (m, 1H), 2.42 (s, 3H), 4.20 (t, *J* = 4.8 Hz, 2H), 4.32 (t, *J* = 5.4 Hz, 1H), 6.51 (d, *J* = 3.3 Hz, 1H), 6.55 (s, 1H), 6.81–6.85 (m, 2H), 7.05 (d, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 15.3, 31.7, 36.1, 63.4, 116.9, 120.2, 124.0, 124.5, 125.4, 128.1, 130.5, 138.5, 146.9, 154.5. Anal. Calcd for $C_{14}H_{14}NOS$: C, 73.01; H, 6.13. Found: C, 72.74; H, 6.22.

4-(*n*-Butyl)-4-phenylchromane (**2.19**): Separated by column chromatography on silica gel with hexanes as solvent, colorless oil; ^{1}H NMR δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.05–1.20 (m, 1H), 1.20–1.40 (m, 3H), 2.02–2.17 (m, 3H), 2.32–2.41 (m, 1H), 3.83 (dt, *J* = 2.1, 11.1 Hz, 1H), 4.14 (dt, *J* = 3.8, 7.8 Hz, 1H), 6.85–6.92 (m, 2H), 7.07–7.19 (m, 5H), 7.23–7.28 (m, 2H); ^{13}C NMR δ 14.0, 23.4, 26.9, 34.9, 40.6, 43.3, 62.8, 117.1, 120.0, 126.0, 126.5, 127.5, 127.6, 128.1, 129.4, 149.8, 155.4. Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.78; H, 8.41.

1-(5-Methylthiophen-2-yl)-1,2,3,4-tetrahydronaphthalene (**2.22c**): Separated by column chromatography on silica gel with hexanes as solvent, colorless oil; ^{1}H NMR δ 1.67–1.71 (m, 1H), 1.81–1.92 (m, 2H), 2.03–2.08 (m, 1H), 2.33 (s, 3H), 2.71–2.78 (m, 2H), 4.21 (t, *J* = 5.9 Hz, 1H), 6.38 (d, *J* = 2.7 Hz, 1H), 6.45 (m, 1H), 6.98–7.05 (m, 4H); ^{13}C NMR δ 15.3, 20.4, 29.4, 33.1, 40.5, 124.3, 124.8, 125.5, 126.2, 129.0, 130.0, 136.8, 137.8, 138.7, 148.7. Anal. Calcd for $C_{15}H_{16}S$: C, 78.90; H, 7.06. Found: C, 78.57; H, 7.07.

1-(4-Methylphenyl)indane (**2.22e**): Separated by column chromatography on silica gel with hexanes/ethyl acetate, 4:1, colorless oil; ^{1}H NMR δ 1.96–2.09 (m, 1H), 2.32 (s, 3H), 2.49–2.59 (m, 1H), 2.86–3.07 (m, 2H), 4.28 (t, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 7.1 Hz, 1H), 7.00–7.24 (m, 6H), 7.26 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR δ 21.0, 31.8, 36.6, 51.2, 124.3, 124.9, 126.3, 126.4, 128.0, 129.1, 135.7, 142.4, 144.2, 147.0. Anal. Calcd for $C_{16}H_{16}$: C, 92.25; H, 7.76. Found: C, 92.05; H, 8.07.

1-*n*-Butyl-1-phenylindane (**2.23**): Separated by column chromatography on silica gel with hexanes/ethyl acetate, 200:1, colorless oil; ^{1}H NMR δ 0.86 (t, *J* = 7.1 Hz, 3H), 1.14–1.36 (m, 4H), 1.94–2.15 (m, 2H), 2.21–2.30 (m, 1H), 2.36–2.45 (m, 1H), 2.82–2.91 (m, 2H), 7.14–7.26 (m, 9H); ^{13}C NMR δ 14.0, 23.4, 27.3, 30.6, 39.9, 40.7, 56.1, 124.6, 125.1, 125.6, 126.0, 126.5, 126.8, 128.0, 144.1, 147.9, 149.1. Anal. Calcd for $C_{19}H_{22}$: C, 91.13; H, 8.87. Found: C, 91.11; H, 9.24.

10-Methyl-9-phenyl-6,7,8,9-tetrahydropyrido[1,2-a]indole (**2.26**): Separated by column chromatography on alumina with hexanes/ethyl acetate, 200:1 as solvent, white microcrystals that turned yellow when exposed to light, mp 93.7–95.7 °C; ^{1}H NMR δ 1.91 (s, 3H), 1.80–1.95 (m, 1H, overlapped), 1.95–2.07 (m, 1H), 2.18–2.23 (m, 1H), 2.16–2.26 (m, 1H), 3.90–3.99 (m, 1H), 4.16–4.23 (m, 1H), 4.43 (t, *J* = 5.0 Hz, 1H), 7.06–7.32 (m, 8H), 7.53 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 8.4, 19.7, 31.0, 39.2, 42.3, 106.5, 108.6, 118.0, 119.0, 120.5, 126.1, 128.0, 128.2, 128.7, 134.0, 135.8, 144.5. Anal. Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.04; H, 7.57; N, 5.32.

9,10-Dimethyl-9-phenyl-6,7,8,9-tetrahydropyrido[1,2-a]indole (**2.27**): Separated by column chromatography on alumina with hexanes as solvent, white microcrystals, mp 88.1–89.7 °C; ^{1}H NMR δ 1.84 (s, 3H), 1.91 (s, 3H), 1.87–2.10 (m, 4H, overlapped), 4.08 (t, *J* = 5.6 Hz, 2H), 7.09–7.30 (m, 8H), 7.51 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 9.9, 20.1, 27.4, 40.8, 41.2, 42.5, 106.2, 108.6, 117.9, 119.0, 120.6, 125.9, 126.6, 128.1, 128.9, 135.2, 138.7, 148.6. Anal. Calcd for $C_{20}H_{21}N$: C, 87.22; H, 7.69; N, 5.09. Found: C, 86.85; H, 7.94; N, 5.09.

2.3.3 Preparation of 1-(3-chloropropyl)-3-methyl-1*H*-indole (2.28e).

A mixture of 3-methylindole (2.66 g, 17 mmol), aqueous sodium hydroxide solution (10%, 10 mL, 30 mmol), 1-bromo-3-chloropropane (1.98 g, 15 mmol), and tetrabutylammonium phosphate (0.17 g, 0.5 mmol) in benzene (10 mL) was heated at reflux for 3 h. The aqueous layer was extracted with benzene (10 mL), and the combined organic layer was washed with hydrochloric acid aqueous solution (10%, 10 mL) and water (10 mL) and then dried (Na_2SO_4). After the solvent was evaporated under reduced pressure, the residue was subjected to column chromatography on silica gel with hexanes (4 drops of pyridine were added for each 200 mL of hexanes to prevent the decomposition of the product). The product was obtained as a colorless oil (2.61 g, 87%) (lit. [94JOC2456] oil); ^{1}H NMR δ 2.10 (qv, *J* = 6.2 Hz, 2H), 2.29 (s, 3H), 3.33 (t, *J* = 6.0 Hz, 2H), 4.14 (t, *J* = 6.3 Hz, 2H), 6.80 (s, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR δ 9.5, 32.7, 41.9, 42.4, 109.0, 110.5, 118.7, 119.0, 121.5, 125.5, 128.8, 136.2.

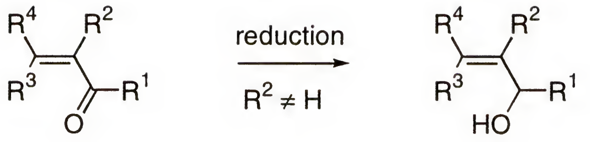
CHAPTER 3
1,4-BROOK REARRANGEMENTS: EFFICIENT SYNTHESES OF SECONDARY AND TERTIARY 2-ARYL- AND 2-HETEROARYL- ALLYL ALCOHOLS

3.1 Introduction

Allyl alcohols are substrates in many important synthetic transformations including sigmatropic processes [91MI827], palladium-catalyzed π-allyl reactions [91MI585] and asymmetric epoxidations [91MI389]. Consequently, numerous syntheses have been developed for allyl alcohols, but due to their great importance, the development of novel synthetic methods remains an active research area.

Most of the methods described in the literature were dealing with the synthesis of allylic alcohols bearing no substituent in the 2-position. There are only a few methods available providing 2-substituted allylic alcohols **3.2** ($R^2 \neq H$, Scheme 3.1).

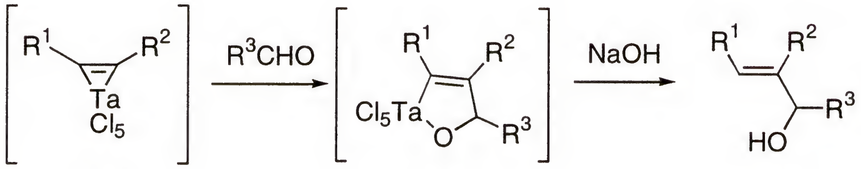
(i) Selective reduction of α,β-unsaturated ketones and aldehydes **3.1** was achieved with zirconocene (Cp_2ZrH_2) and hafnocene (Cp_2HfH_2) complexes [88JOC3752], with silica gel supported zinc borohydride [91JOC4796], or by lithium pyrrolidinoborohydride [93TL257]. However, these methods suffer from the limited availability of the requisite α-substituted α,β-unsaturated ketones or aldehydes **3.1** (Scheme 3.1).



3.1 **3.2**

Scheme 3.1

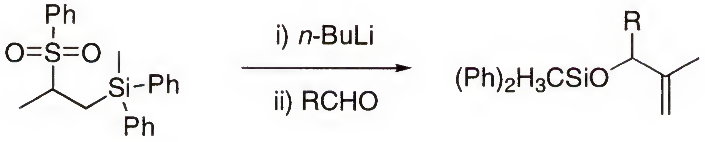
(ii) Trisubstituted allylic alcohols **3.5** were prepared from tantalum-alkyne complexes **3.3** generated *in situ* and aldehydes [90JOC1707]. This transition metal mediated method is occasionally plagued with poor regioselectivity and suffers from the availability of the requisite alkynes.



3.3 **3.4** **3.5**

Scheme 3.2

(iii) The [1,4]-C→O silicon rearrangement [80MI149] was used for the syntheses of two 2-alkyl-substituted allylic alcohols **3.7** (Scheme 3.3) [95S78]. However, no examples for the analogous synthesis of the corresponding 2-aryl derivatives are known so far, presumably because their is no straightforward method for the preparation of the starting materials required.



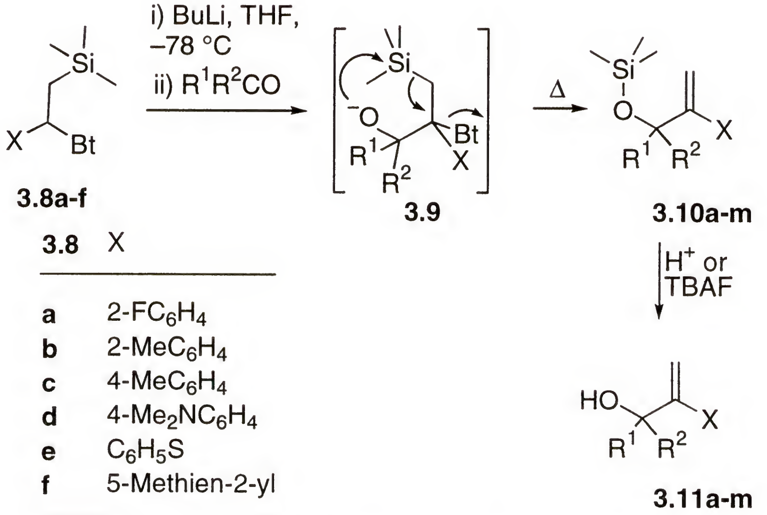
3.6 **3.7**

Scheme 3.3

Preliminary results about the application of new α-arylalkenyllithium reagents for the synthesis of secondary allylic alcohols possessing a 2-aryl substituent have been published recently by our group [97JA9321]. A detailed account of this work together with the extension of our methodology is presented herein.

3.2 Results and Discussion

Reagents **3.8a-c** were prepared as previously described [97JA9321]. Three novel reagents **3.8d-f** were prepared in analogy to **3.8a-c** in high yields and multi-gram-scale. Compounds **3.10b-d** and **3.10h** (Table 3.1) were already described in a preliminary publication [97JA9321] focusing on the reactions of nonenolizable aldehydes. The work reported here, however, aimed at the extension of this methodology towards the use of enolizable or bulky aldehydes and ketones as well as further modification of the X-group (Scheme 3.4).



3.8a-f

3.9

3.10a-m

3.11a-m

3.8	X
a	2-FC_6H_4
b	2-MeC_6H_4
c	4-MeC_6H_4
d	4-$Me_2NC_6H_4$
e	C_6H_5S
f	5-Methien-2-yl

For the significance of X, R^1 and R^2 in **3.10**, **3.11** see Table 3.1

Scheme 3.4

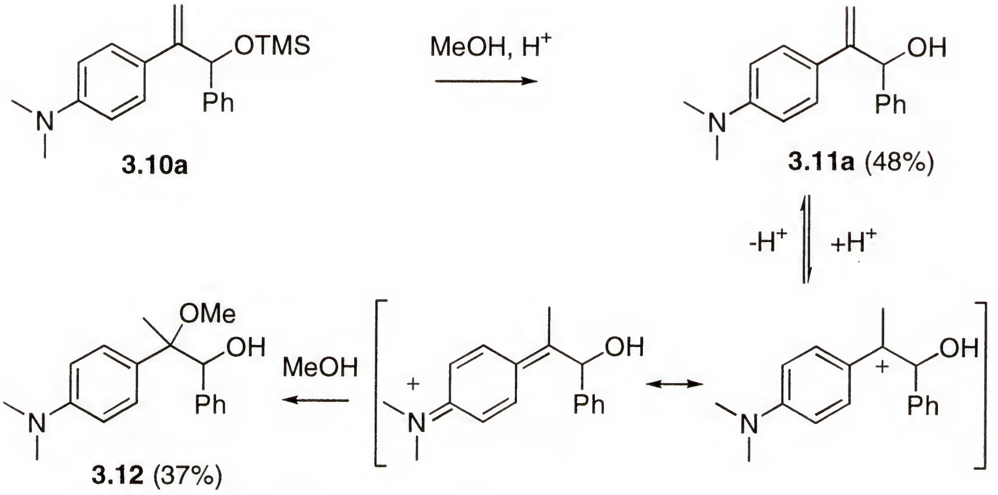
Table 3.1. Synthesis of Trimethylsilyl Allyl Ethers **3.10a-m** and Allyl Alcohols **3.11a-m**.

	X	R^1	R^2	Reaction Conditions		Yield %	
				temp(°C) /time(h)[a]	Solvent/additive/ time(h)[b]	**3.10**	**3.11**
a	4-$\mathrm{Me_2NC_6H_4}$	H	Ph	105/7	MeOH/$\mathrm{H^+}$/2	52	48[f]
b	2-$\mathrm{FC_6H_4}$	H	3-$\mathrm{MeOC_6H_4}$	rt/16	/	52	/
c	4-$\mathrm{MeC_6H_4}$	H	3-$\mathrm{MeOC_6H_4}$	rt/16	/	72	/
d	4-$\mathrm{MeC_6H_4}$	H	*t*-Bu	rt/16	/	87	/
e	2-$\mathrm{MeC_6H_4}$	H	2-$\mathrm{MeOC_6H_4}$	115/8	/	53[c,d]	46[c,d]
f	2-$\mathrm{FC_6H_4}$	H	2-$\mathrm{MeOC_6H_4}$	90/5	/	22[c]	40[c]
g	5-Methien-2-yl	H	2-$\mathrm{MeOC_6H_4}$	81/24	silica gel	0[c]	56[c]
h	2-$\mathrm{MeC_6H_4}$	H	3-$\mathrm{MeOC_6H_4}$	rt/16	THF/TBAF/2	/	70[g]
i	2-$\mathrm{FC_6H_4}$	H	$\mathrm{CH_2CH_2C_6H_5}$	rt/16	MeOH/$\mathrm{H^+}$/1	77	97
j	2-$\mathrm{FC_6H_4}$	–$\mathrm{(CH_2)_5}$–		rt/16	MeOH/$\mathrm{H^+}$/1	75[e]	100
k	2-$\mathrm{FC_6H_4}$	H	*i*-Pr	rt/16	THF/TBAF/3.5	67[e]	79
l	2-$\mathrm{FC_6H_4}$	H	*c*-$\mathrm{C_6H_{11}}$	115/24	THF/TBAF/4	67	93
m	2-$\mathrm{FC_6H_4}$	H	$\mathrm{CH(CH_3)Ph}$	120/1	MeOH/$\mathrm{H^+}$/1	56	97

[a] The deprotonation of the benzotriazole derivatives **3.8** and the addition of the carbonyl compounds were performed at –78 °C. The reaction conditions listed in the table refer to the rearrangement step. [b] The reaction conditions listed in the table refer to the desilylation step. [c] Significant *O*-desilylation was observed and the free allyl alcohol was isolated. [d] Yield calculated on recovered material. [e] $\mathrm{CeCl_3}$ (1 equiv) was added before the addition of the carbonyl compounds. [f] Significant addition of methanol to the double bond was observed. [g] Overall yield without isolation of **3.10h**.

Compound **3.10a** was successfully synthesized in analogy to the literature procedure [97JA9321], i.e. by deprotonating **3.8a** with *n*-BuLi at –78 °C followed by the addition of benzaldehyde. Then the reaction mixture was allowed to warm up to rt over

16 h. Finally the solvent was removed and the residue was heated to 105 °C for 7 h. An attempt to desilylate **3.10a** by refluxing it with methanol and *p*-toluenesulfonic acid not only provided the desired allylic alcohol **3.11a** but also the by-product **3.12** (Scheme 3.5). A reasonable explanation for this is that the double bond was first protonated according to Markovnikov's rule to give a carbocation additionally stabilized by the *p*-dimethylamino group which was then trapped by the nucleophilic addition of methanolate providing the β-methoxy alcohol **3.12** (Scheme 3.5).

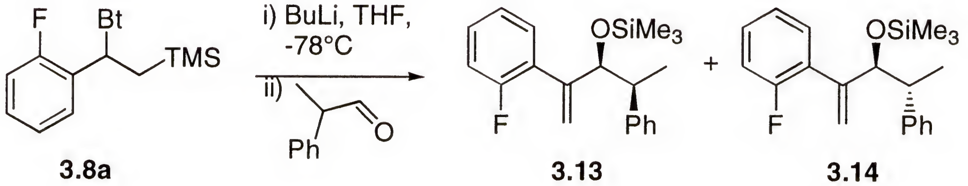


Scheme 3.5

Analogous reactions of **3.8a,b,f** with 2-methoxybenzaldehyde resulted in the formation of the *O*-silylated compounds **3.10e-g** together with the corresponding free allylic alcohols (Table 3.1). Chromatography on silica gel of the crude mixtures resulting from the reactions of **3.8a** and **3.8b** gave the pure alcohols **3.11e,f** and the corresponding silyl ethers **3.10e,f**, respectively. However, the chromatographic purification of the crude mixture resulting from the reaction of **3.8g** only provided the alcohol **3.11g**, presumably due to complete desilylation during work-up or column chromatogaphy on silica gel.

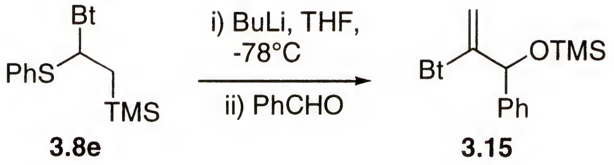
Our method was also applied successfully to analogous reactions employing enolizable aldehydes and an enolizable ketone (cyclohexanone). The corresponding *O*-silylated compounds **3.10i-m** and the free allylic alcohols **3.11i-m** were obtained in excellent yields. In two cases (the synthesis of **3.10j** and **3.10k**), CeCl$_3$ [91MI231, 96TL6787, 96JA4581] was added to diminish the basicity of the benzotriazole-stablilized carbanion to avoid the enolization of the carbonyl compounds. It should be noted that the use of acetophenone and α-tetralone (both with and without addition of CeCl$_3$) did not provide the desired products, presumably due to their higher C-H acidity.

We also performed a reaction using an aldehyde with a stereogenic center (Scheme 3.6). According to the ^{1}H NMR and GC-MS spectra the crude mixture contained both diastereomers of the *O*-silylated compound **3.10m** (the syn-diastereomer **3.13** and the anti-diastereomer **3.14**) in a 13.3 : 1 ratio (determined by GC-MS). On the basis of Felkin's rule [95MI1151] we have tentatively assigned structure **3.13** to be the major product which was isolated as a sole diastereomer after chromatography in 56 % yield.



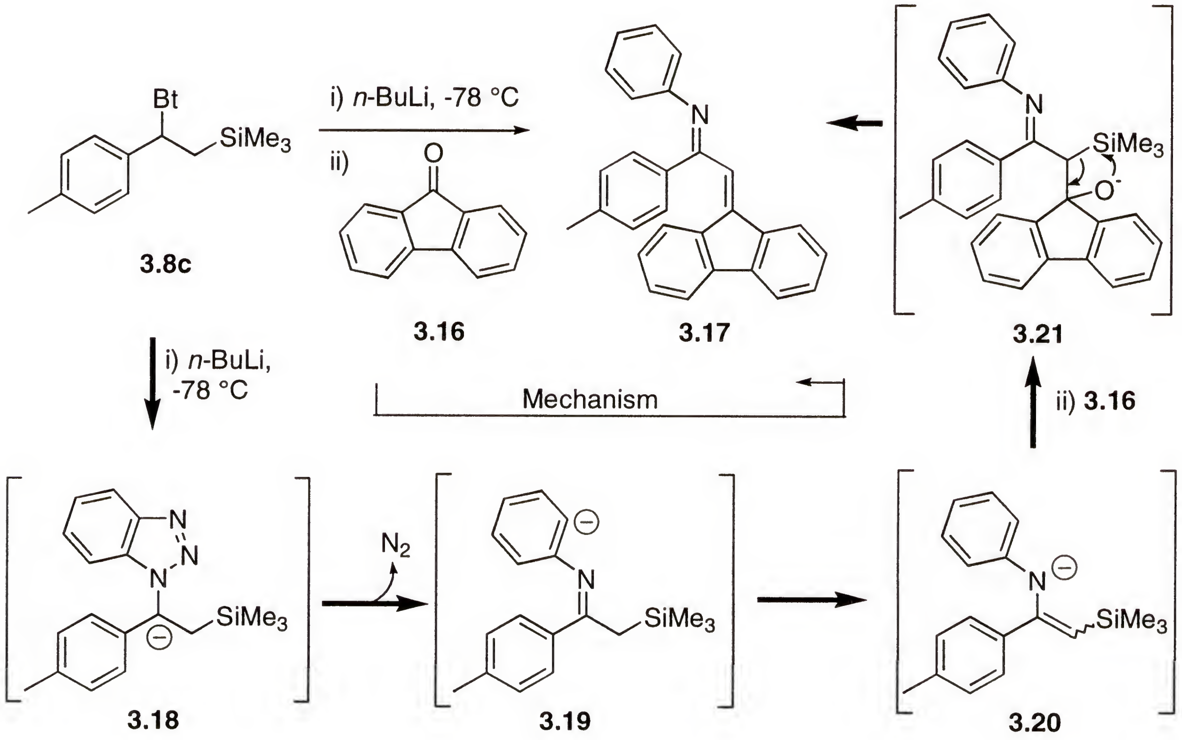
Scheme 3.6

Deprotonation of compound **3.8e**, followed by the addition of benzaldehyde furnished product **3.15** in 70% yield resulting from elimination of the thiophenolate group instead of the benzotriazolate group (Scheme 3.7).



Scheme 3.7

Surprisingly, an attempt to react 9-fluorenone (**3.16**) with carbanion **3.18** provided the unsaturated *N*-Phenylimine **3.17**. This can be rationalized by the mechanism depicted in Scheme 3.8. Presumably, the ketone **3.16** was sterically too demanding to react with the relatively bulky carbanion **3.18**. As a consequence, **3.18** decomposed with increasing temperature under formation of N_2 to give the anion **3.19**, followed by intramolecular deprotonation furnishing the enamide **3.20**. Subsequently, **3.20** reacted with 9-fluorenone (**3.16**) to form intermediate **3.21**, which then rearranged to yield the final product **3.17**.



Scheme 3.8

Compound **3.17** was unambiguously characterized by ^{1}H and ^{13}C NMR spectra, X-ray structure determination (Figure 3.1) and CHN analysis.

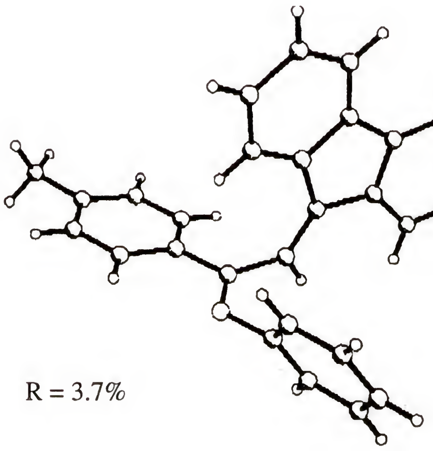


Figure 3.1

In conclusion, we have developed a mild, straightforward and highly efficient synthesis of secondary and tertiary 2-aryl and 2-heteroaryl substituted allylic alcohols and their *O*-trimethylsilyl derivatives. Its broad scope as well as the easy access to the starting materials should make our methodology widely applicable in organic synthesis.

3.2 Experimental Section

Melting points were determined with a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer and are uncorrected. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (300 MHz) or $CDCl_3$ as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel (230–400 mesh).

3.3.1 General Procedure for the Synthesis of Compounds 3.8d-f.

n-BuLi (1.6 M, 2.5 mL, 4 mmol) was added to a solution of the corresponding 1-{1-[(trimethylsilyl)methyl]prop-2-enyl}-1*H*-1,2,3-benzotriazole (0.98 g, 4 mmol) in THF (50 mL) at –78 °C under argon. After 15 min stirring, a solution of the appropriate alkyl halide (4.1 mmol) was added. The reaction mixture was allowed to warm to rt overnight, before being washed with brine (2 × 20 mL), extracted with ethyl ether (2 × 20 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give an oil. The crude product was subjected to flash column chromatography with hexanes : ethyl ether = 3 : 1 to give pure compounds **3.8**.

4-[1-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(trimethylsilyl)ethyl]-*N*,*N*-dimethylaniline (3.8d): White microcrystals (89% yield), mp 134.9–136.2 °C; ^{1}H NMR δ 0.13 (s, 9H), 1.94–2.13 (m, 2H), 2.91 (s, 6H), 5.96 (t, J = 8.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 7.26–7.38 (m, 4H), 7.45 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H); ^{13}C NMR δ –1.6, 23.3, 40.3, 61.1, 110.3, 112.2, 119.8, 123.5, 126.6, 127.8, 128.0, 132.1, 146.4, 150.2. Anal. Calcd for $C_{19}H_{26}N_4Si$: C, 67.41; H, 7.74; N, 16.55. Found: C, 67.45; H, 7.44; N, 16.61.

1-[1-Phenylthio-2-(trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole (3.8e): Yellow prisms (74% yield), mp 64.5–65.5 °C; ^{1}H NMR δ –0.01 (s, 9H), 1.70–1.79 (m, 1H), 1.92–2.00 (m, 1H), 6.32–6.37 (m, 1H), 7.00–7.16 (m, 5H), 7.34 (t, J = 7.9 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ –1.8, 23.7, 65.6, 111.3, 120.0, 123.8, 126.8, 128.6, 128.8, 131.2, 131.7, 133.3, 146.6. Anal. Calcd for $C_{17}H_{21}N_3SSi$: C, 62.34; H, 6.46; N, 12.83. Found: C, 62.44; H, 6.66; N, 12.79.

1-[1-(5-Methylthiophen-2-yl)-2-(trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole (3.8f): Light yellow prisms (90% yield), mp 78.4–80.3 °C (hexanes); ^{1}H NMR δ –0.15 (s, 9H), 1.93 (dd, J = 14.6, 7.4 Hz, 1H), 2.05 (dd, J = 14.6, 8.8 Hz, 1H), 2.38 (s, 3H), 6.28 (t, J = 8.0 Hz, 1H), 6.56 (d, J = 2.3 Hz, 1H), 6.88 (d, J = 3.3 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.0 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ –1.8, 15.2, 24.1, 57.0, 110.3, 120.0, 123.7, 124.6, 125.4, 126.9, 131.6, 140.3, 141.9, 146.5. Anal. Calcd for $C_{16}H_{21}N_3SSi$: C, 60.91; H, 6.71; N, 13.32. Found: C, 61.29; H, 6.86; N, 12.97.

3.3.2 General Procedure for the Synthesis of Compounds 3.10a-f, 3.10i-m, 3.11e-h, 3.15 and 3.17.

The corresponding benzotriazole derivative **3.8** (2 mmol) was dissolved in THF (20 mL), cooled to –78 °C and *n*-BuLi in hexane (1.6 M, 1.25 mL, 2 mmol) was added. For the preparation of compounds **3.10j,k**, anhydrous cerium(III) chloride (0.493 g, 2 mmol) was added. After 30 min stirring, an aldehyde or ketone (2 mmol) was added and the mixture was allowed to warm to rt over 16 h. In the case of compounds **3.10a,e-g** and **3.10l,m** the solvent was distilled off under a stream of argon and the remaining oil was heated at the temperature and for the time indicated in Table 3.1 followed by the addition of methylene chloride (40 mL). The resulting solution was washed with brine (2 × 20 mL) and dried in case of compounds **3.10b-d** and **3.15**. In case of **3.10a** and **3.10e-m** the reaction mixture was washed with an aqueous sodium hydroxide solution (2 M, 40 mL) and dried. After removal of the solvent in vacuo the remaining oil was subjected to flash column chromatography with hexanes : diethyl ether = 5 : 1, in the case of **3.10b-d** and

3.15 to give the pure products. For all other cases the chromatographic system is indicated individually. Compounds **3.11e** and **3.11f** were obtained together with **3.10e** and **3.10f**. Compound **3.11g** was obtained without **3.10g** due to desilylation. For **3.11h**, the crude oil of **3.10h** was dissolved in a THF-solution of TBAF (1 M, 2.4 mL, 2.4 mmol) and stirred at rt for 2 h. After the removal of the solvent *in vacuo*, the remaining oil was subjected to flash column chromatography with 1:1 hexanes/diethyl ether to give the pure product **3.11h**.

***N*,*N*-Dimethyl-4-(1-phenyl[(trimethylsilyl)oxy]methylethenyl)aniline (3.10a):** Purified by column chromatography with hexanes : ethyl acetate = 50 : 1, yellow oil (52% yield); ^{1}H NMR δ 0.60 (s, 9H), 3.28 (s, 6H), 5.86 (s, 1H), 5.87 (s, 1H), 6.10 (s, 1H), 7.10 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 7.1 Hz, 2H), 7.67–7.71 (m, 3H), 7.84 (d, J = 7.4 Hz, 2H); ^{13}C NMR δ 0.1, 40.2, 76.8, 111.1, 111.8, 126.7, 126.8, 127.3, 120.5, 127.8, 128.0, 143.1, 149.7, 150.0. Anal. Calcd for $C_{20}H_{27}NOSi$: C, 73.79; H, 8.36; N, 4.30. Found: C, 73.51; H, 8.53; N, 4.40.

{[2-(2-Fluorophenyl)-1-(3-methoxyphenyl)allyl]oxy}(trimethyl)silane (3.10b): Colorless oil (52% yield); ^{1}H NMR δ 0.11 (s, 9H), 3.71 (s, 3H), 5.35 (s, 1H), 5.44 (s, 1H), 5.54 (s, 1H), 6.71–6.73 (m, 1H), 6.84–6.90 (m, 4H), 7.14 (t, J = 8.3 Hz, 1H), 7.21–7.26 (m, 2H); ^{13}C NMR δ 0.0, 55.0, 77.0, 112.4 (d, J = 5.9 Hz), 114.3, 114.5, 114.8, 119.1, 129.0 (d, J = 7.1 Hz), 135.5, 144.1, 149.8, 159.5, 162.1 (d, J = 244.6 Hz). Anal. Calcd for $C_{19}H_{23}FO_2Si$: C, 69.06; H, 7.01. Found: C, 69.17; H, 7.34.

{[1-(3-Methoxyphenyl)-2-(4-methylphenyl)-allyl]oxy}(trimethyl)silane (3.10c): Colorless oil (72% yield); ^{1}H NMR δ 0.11 (s, 9H), 2.27 (s, 3H), 3.74 (s, 3H), 5.40 (s, 1H), 5.44 (s, 1H), 5.57 (s, 1H), 6.72 (dd, J = 8.4 and 1.8 Hz, 1H), 6.89–6.91 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.13–7.20 (m, 3H); ^{13}C NMR δ 0.1, 21.0, 55.0, 76.7, 112.5, 113.5, 119.3, 127.1, 128.6, 128.9, 136.7, 136.9, 144.5, 150.5, 159.5. Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.97; H, 8.31.

{[1-*t*-Butyl-2-(4-methylphenyl)-allyl]oxy}(trimethyl)silane (3.10d): Colorless oil (87% yield); ^{1}H NMR δ 0.15 (s, 9H), 0.73 (s, 9H), 2.33 (s, 3H), 4.34 (s, 1H), 5.28 (s, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 0.3, 21.1, 26.7, 36.5, 81.3, 115.9, 126.7, 128.9, 136.7, 140.3, 150.5. Anal. Calcd for $C_{17}H_{28}OSi$: C, 73.85; H, 10.21. Found: C, 74.08; H, 10.42.

Trimethyl[1-[2-(methyloxy)phenyl]-2-(2-methylphenyl)prop-2-enyl]oxysilane (3.10e): Yellow oil (53% yield); ^{1}H NMR δ 0.39 (s, 9H), 2.60 (s, 3H), 3.97 (s, 3H), 5.32 (s, 1H), 5.75 (s, 1H), 6.25 (s, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.31–7.63 (m, 6H), 7.86 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR δ −0.21, 19.5, 55.2, 70.2, 110.1, 113.3, 120.4, 124.6, 126.6, 127.9, 128.0, 129.4, 129.6, 131.1, 135.9, 140.8, 151.4, 159.0. Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.51; H, 8.44.

{2-(2-Fluorophenyl)-1-[2-(methyloxy)phenyl]prop-2-enyloxy}(trimethyl)-silane (3.10f): Purified by column chromatography with hexanes : ethyl acetate = 50 : 1, colorless oil (22% yield); ^{1}H NMR δ 0.22 (s, 9H), 3.81 (s, 3H), 5.39 (s, 1H), 5.70 (s, 1H), 6.25 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.04–7.16 (m, 3H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.30–7.35 (m, 2H), 7.59 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ –0.1, 55.2, 69.0, 110.2, 115.1 (d, *J* = 22.7 Hz), 115.3, 120.5, 123.4 (d, *J* = 3.4 Hz), 128.2 (d, *J* = 13.4 Hz), 128.5 (d, *J* = 8.1 Hz), 130.9 (d, *J* = 4.4 Hz), 147.0, 156.3, 160.0 (d, *J* = 245.1 Hz). Anal. Calcd for $C_{19}H_{23}FO_2Si$: C, 69.05; H, 7.02. Found: C, 69.08; H, 7.31.

[2-(2-Fluorophenyl)-1-(2-phenylethyl)prop-2-enyl]oxy(trimethyl)silane (3.10i): Purified by column chromatography with hexanes : ethyl acetate = 100 : 1, colorless oil (75% yield); ^{1}H NMR δ 0.19 (s, 9H), 1.60–1.83 (m, 2H), 2.50–2.60 (m, 1H), 2.70–2.80 (m, 1H), 4.62–4.64 (m, 1H), 5.20 (s, 1H), 5.57 (s, 1H), 6.99–7.14 (m, 4H), 7.19–7.26 (m, 5H); ^{13}C NMR δ 0.1, 31.8, 38.4, 73.7, 115.4, 115.7, 124.0 (d, J = 3.3 Hz), 125.6, 128.2, 128.4, 129.0 (d, J = 8.1 Hz), 130.8 (d, J = 4.4 Hz), 142.3, 147.5, 159.7 (d, J = 245.1 Hz). Anal. Calcd for $C_{20}H_{25}FOSi$: C, 73.13; H, 7.67. Found: C, 72.85; H, 7.87.

{1-[1-(2-Fluorophenyl)ethenyl]cyclohexyloxy}(trimethyl)silane (3.10j): Purified by column chromatography with hexanes, colorless oil (75% yield); ^{1}H NMR δ –0.19 (s, 9H), 0.84–0.90 (m, 1H), 1.09 (br s, 3H), 1.16–1.36 (m, 7H), 4.74 (s, 1H), 5.24 (s, 1H), 6.61–6.69 (m, 2H), 6.80–6.87 (m, 1H), 6.90–6.96 (m, 1H); ^{13}C NMR δ 2.8, 22.6, 25.6, 37.8, 77.7, 115.3 (d, J = 23.3 Hz), 116.8, 123.0 (d, J = 3.2 Hz), 128.4 (d, J = 8.0 Hz), 129.5 (d, J = 16.2 Hz), 131.7 (d, J = 3.5 Hz), 149.8, 159.8 (d, J = 243.5 Hz). Anal. Calcd for $C_{17}H_{25}FOSi$: C, 69.81; H, 8.63. Found: C, 69.72; H, 8.89.

[2-(2-Fluorophenyl)-1-(1-methylethyl)prop-2-enyl]oxy(trimethyl)silane (3.10k): Purified by column chromatography with hexanes, colorless oil (67% yield); ^{1}H NMR δ –0.22 (s, 9H), 0.38 (d, J = 6.8 Hz, 3H), 0.48 (d, J = 6.6 Hz, 3H), 1.04–1.18 (m, 1H), 4.01 (s, 1H), 4.82 (s, 1H), 5.09 (d, J = 1.7 Hz, 1H), 6.59–6.71 (m, 2H), 6.80–6.90 (m, 2H); ^{13}C NMR δ 0.2, 15.4, 20.2, 31.4, 78.6, 115.6 (d, J = 22.8 Hz), 116.3, 123.9 (d, J = 3.5 Hz), 128.8 (d, J = 8.1 Hz), 128.9, 130.6 (d, J = 4.5 Hz), 146.6, 159.8 (d, J = 244.8 Hz). Anal. Calcd for $C_{15}H_{23}FOSi$: C, 67.62; H, 8.70. Found: C, 67.75; H, 9.03.

[1-Cyclohexyl-2-(2-fluorophenyl)prop-2-enyl]oxy(trimethyl)silane (3.10l): Purified by column chromatography with hexanes : ethyl acetate = 100 : 1, colorless oil

(67% yield); ^{1}H NMR δ 0.17 (s, 9H), 1.07–1.16 (m, 6H), 1.50–1.71 (m, 5H), 4.37 (s, 1H), 5.23 (s, 1H), 5.47 (s, 1H), 7.00–7.12 (m, 2H), 7.21–7.31 (m, 2H); ^{13}C NMR δ 0.2, 26.2, 26.2, 26.5, 26.5, 30.7, 41.4, 78.7, 115.6 (d, J = 23.0 Hz), 116.5, 123.9 (d, J = 3.3 Hz), 128.7 (d, J = 8.3 Hz), 128.9, 130.6 (d, J = 4.4 Hz), 146.0, 159.8 (d, J = 249.0 Hz). Anal. Calcd for $C_{18}H_{27}FOSi$: C, 70.54; H, 8.88. Found: C, 70.41; H, 9.04.

2-(2-Fluorophenyl)-1-(1-phenylethyl)prop-2-enyl trimethylsilyl ether (3.10m): Separated by column chromatography with hexanes : ethyl acetate = 50 : 1, colorless oil (56% yield); ^{1}H NMR δ 0.14 (s, 9H), 1.45 (d, J = 6.9 Hz, 3H), 2.93–3.00 (m, 1H), 5.04 (s, 1H), 5.55 (s, 1H), 5.85 (s, 1H), 7.32–7.45 (m, 4H), 7.49–7.59 (m, 4H); ^{13}C NMR δ –0.4, 11.8, 42.6, 78.0 (d, J = 3.9 Hz), 115.7 (d, J = 22.9 Hz), 116.4, 124.2 (d, J = 3.4 Hz), 126.0, 127.9, 128.2, 129.0 (d, J = 8.2 Hz), 130.5 (d, J = 18.3 Hz), 145.1, 146.7, 159.7 (d, J = 244.7 Hz). Anal. Calcd for $C_{20}H_{25}FOSi$: C, 73.13; H, 7.67. Found: C, 73.44; H, 7.96.

1-[2-(Methyloxy)phenyl]-2-(2-methylphenyl)prop-2-en-1-ol (3.11e): Colorless oil (46% yield); ^{1}H NMR δ 2.41 (s, 3H), 3.23 (d, J = 6.7 Hz, 1H), 3.94 (s, 3H), 5.27 (s, 1H), 5.68 (s, 1H), 5.90 (d, J = 6.7 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.28–7.35 (m, 3H), 7.43–7.49 (m, 2H); ^{13}C NMR δ 19.4, 55.2, 73.5, 110.7, 113.8, 120.6, 124.9, 126.9, 128.2, 128.6, 129.2, 129.8, 135.7, 140.3, 150.8, 156.9. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.12; H, 7.29.

2-(2-Fluorophenyl)-1-[2-(methyloxy)phenyl]prop-2-en-1-ol (3.11f): Yellow oil (40% yield); ^{1}H NMR δ 3.12 (d, J = 5.3 Hz, 1H), 3.90 (s, 3H), 5.49 (s, 1H), 5.69 (s, 1H), 6.04 (br s, 1H), 6.95–7.05 (m, 2H), 7.10–7.17 (m, 2H), 7.27–7.44 (m, 4H); ^{13}C NMR δ 55.3, 71.9 (d, J = 3.0 Hz), 110.7, 115.3 (d, J = 22.7 Hz), 116.0, 123.6 (d, J = 3.4 Hz), 128.1, 128.4, 128.8 (d, J = 6.2 Hz), 129.8, 130.4 (d, J = 4.4 Hz), 146.2, 157.0, 159.7 (d, J = 245.4 Hz). Anal. Calcd for $C_{16}H_{15}FO_2$: C, 74.40; H, 5.85. Found: C, 74.50; H, 5.98.

1-[2-(Methyloxy)phenyl]-2-(5-methylthiophen-2-yl)prop-2-en-1-ol (3.11g): Purified by column chromatography with hexanes : ethyl acetate = 3 : 1, dark-red oil (56% yield); ^{1}H NMR δ 2.41 (s, 3H), 2.68 (d, J = 4.9 Hz, 1H), 3.89 (s, 3H), 5.29 (s, 1H), 5.57 (s, 1H), 5.98 (d, J = 4.7 Hz, 1H), 6.54 (d, J = 2.8 Hz, 1H), 6.77 (d, J = 3.4 Hz, 1H), 6.90–6.94 (m, 2H), 7.24–7.34 (m, 2H); ^{13}C NMR δ 15.3, 55.5, 69.8, 110.6, 111.1, 120.8, 124.2, 125.4, 128.0, 129.1, 129.9, 138.8, 140.6, 142.8, 157.1. HRMS calcd (FAB) for $C_{15}H_{16}O_2S$: 260.0810, Found: 260.0863.

1-(3-Methoxyphenyl)-2-(2-methylphenyl)-2-propen-1-ol (3.11h): Colorless oil (70% yield); ^{1}H NMR δ 2.07 (s, 3H), 2.58 (br s, 1H), 3.65 (s, 3H), 5.01 (s, 1H), 5.30 (s, 1H), 5.56 (s, 1H), 6.73–6.79 (m, 3H), 6.86 (d, J = 7.2 Hz, 1H), 6.99–7.15 (m, 4H); ^{13}C NMR δ 19.5, 55.0, 77.2, 112.0, 113.4, 113.9, 119.1, 125.0, 127.1, 129.0, 129.1, 129.9, 135.8, 139.5, 143.2, 150.9, 159.3. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.09; H, 7.48.

{[2-[1-(1,2,3-Benzotriazol-1-yl)]-1-(phenyl)allyl]oxy}(trimethyl)silane (3.15): Colorless oil (70% yield); ^{1}H NMR δ 0.08 (s, 9H), 5.53 (s, 1H), 5.60 (s, 1H), 6.16 (s, 1H), 7.13–7.20 (m, 3H), 7.29–7.34 (m, 3H), 7.38–7.48 (m, 2H), 8.00 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ – 0.1, 74.2, 107.8, 110.5, 119.8, 124.0, 126.7, 127.8, 127.9, 128.1, 132.9, 140.4, 145.7, 146.4. Anal. Calcd for $C_{18}H_{21}N_3OSi$: C, 66.84; H, 6.89; N, 12.99. Found: C, 66.51; H, 6.89; N, 13.06.

***N*-[(E)-2-(9*H*-Fluoren-9-ylidene)-1-(4-methylphenyl)ethylidene]aniline (3.17):** Purified by column chromatography on silica gel by hexanes : ethyl ether (5:1), yellow prism (67% yield), mp 176.1–177.0 °C; ^1H NMR δ 2.35 (s, 3H), 6.90–7.06 (m, 5H), 7.13–7.35 (m, 7H), 7.41 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.60–7.64 (m, 2H), 7.94 (d, J = 7.7 Hz, 2H); ^{13}C NMR δ 21.4, 119.7, 120.2, 120.7, 120.9, 124.1, 125.6, 127.1, 127.2, 128.4, 128.6, 128.9, 129.0, 129.4, 134.8, 135.9, 137.8, 139.7, 140.3, 141.2, 141.4, 151.0, 165.2. Anal. Calcd for $C_{28}H_{21}N$: C, 90.53; H, 5.70; N, 3.77. Found: C, 90.52; H, 5.71; N, 3.46.

3.3.3 General Procedure for the Preparation of Compounds 3.11a, 3.11i, 3.11j, 3.11m and 3.12.

The trimethylsilyl ether **3.10a,** or **3.10i,j,m** (1 mmol) was dissolved in methanol (24 mL) and *p*-toluenesulfonic acid monohydrate (0.08 g, 0.4 mmol) was added. The reaction mixture was stirred at rt for 1h and the excess methanol was removed under reduced pressure. The residue was dissolved in methylene chloride (20 mL). The solution was washed with saturated aqueous sodium bicarbonate solution (20 mL) and water (20 mL), and was dried (Na_2SO_4). Finally, the solvent was removed under reduced pressure to give the pure product.

2-[4-(Dimethylamino)phenyl]-1-phenylprop-2-en-1-ol (3.11a): Microcrystals, mp 88.6–90.0 °C, (48% yield); ^1H NMR δ 2.26 (br s, 1H), 2.88 (s, 6H), 5.28 (s, 1H), 5.43 (s, 1H), 5.66 (s, 1H), 6.59 (d, J = 8.3 Hz, 2H), 7.21–7.32 (m, 5H), 7.41 (d, J = 6.8 Hz, 2H); ^{13}C NMR δ 40.3, 75.7, 110.9, 112.1, 126.8, 126.9, 127.4, 127.5, 128.3, 142.2, 149.6, 150.0. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.48; H, 7.87; N, 5.57.

2-(2-Fluorophenyl)-5-phenylpent-1-en-3-ol (3.11i): Colorless oil (97% yield); ^1H NMR 1.57–1.81 (m, 2H), 2.19 (br s, 1H), 2.50–2.75 (m, 2H), 4.48 (t, J = 6.6 Hz, 1H), 5.14 (s, 1H), 5.47 (s, 1H), 6.88–7.11 (m, 9H); ^{13}C NMR δ 31.6, 37.4, 73.2, 115.4, 115.7, 124.0 (d, *J* = 3.3 Hz), 125.7, 127.8 (d, *J* = 15.1 Hz), 128.3 (d, *J* = 7.6 Hz), 129.1 (d, *J* = 8.1 Hz), 130.5 (d, *J* = 3.8 Hz), 141.8, 147.5, 159.6 (d, *J* = 244.5 Hz). Anal. Calcd for $C_{17}H_{17}FO$: C, 79.66; H, 6.69. Found: C, 79.38; H, 6.91.

1-[1-(2-Fluorophenyl)ethenyl]cyclohexanol (3.11j): Colorless oil (100% yield); ^{1}H NMR δ 1.08–1.20 (m, 1H), 1.52–1.73 (m, 10H), 5.03 (s, 1H), 5.58 (s, 1H), 7.01–7.11 (m, 2H), 7.16–7.29 (m, 2H); ^{13}C NMR δ 21.8, 25.4, 36.3, 73.6, 114.9, 115.2 (d, *J* = 23.3 Hz), 123.2 (d, *J* = 3.3 Hz), 128.7 (d, *J* = 8.0 Hz), 128.9, 131.7 (d, *J* = 4.0 Hz), 151.6, 159.6 (d, *J* = 242.2 Hz). Anal. Calcd for $C_{14}H_{17}FO$: C, 76.33; H, 7.78. Found: C, 76.19; H, 8.03.

2-(2-Fluorophenyl)-4-phenylpent-1-en-3-ol (3.11m): Colorless oil (97% yield); ^{1}H NMR δ 1.21 (d, *J* = 6.9 Hz, 3H), 1.87 (br s, 1H), 2.78–2.81 (m, 1H), 4.81 (br s, 1H), 5.30 (s, 1H), 5.61 (s, 1H), 7.01–7.28 (m, 9H); ^{13}C NMR δ 12.9, 42.8, 77.0, 115.7 (d, *J* = 22.7 Hz), 116.5, 124.2 (d, *J* = 3.3 Hz), 126.4, 127.9, 128.3, 129.2 (d, *J* = 8.2 Hz), 130.4 (d, *J* = 4.4 Hz), 144.3, 146.2, 159.7 (d, *J* = 245.0 Hz). Anal. Calcd for $C_{17}H_{17}FO$: C, 79.66; H, 6.69. Found: C, 79.79; H, 6.91.

2-[4-(Dimethylamino)phenyl]-2-(methyloxy)-1-phenylpropan-1-ol (3.12): White powder (37% yield); ^{1}H NMR δ 3.12 (s, 6H), 3.27 (s, 3H), 3.62 (s, 1H), 4.95 (s, 1H), 6.81 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 7.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.26–7.28 (m, 3H); ^{13}C NMR δ 14.0, 40.5, 50.2, 81.8, 82.8, 111.8, 127.0, 127.0, 127.5, 128.5, 138.9, 149.9. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.34; H, 8.21; N, 4.96.

3.3.4 General Procedure for the Preparation of Compounds 3.11k,l.

The trimethylsilyl ether **3.10l** or **3.10k** (0.5 mmol) was dissolved in THF (30 mL) followed by the addition of a THF-solution of TBAF (1 M, 0.7 mL, 0.7 mmol). The reaction mixture was stirred at rt for the time given in Table 3.1. The solvent was removed under reduced pressure and the remaining oil was dissolved in methylene chloride. The organic layer was washed with dilute aqueous hydrochloric acid solution (8%, 3 × 10 mL), water (10 mL) and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was distilled with a Kugelrohr apparatus at 0.4 Torr and 110 °C.

2-(2-Fluorophenyl)-4-methylpent-1-en-3-ol (3.11k): Colorless oil (79% yield); ^{1}H NMR δ 0.86 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 1.62–1.70 (m, 1H), 2.00 (br s, 1H), 4.41 (d, J = 4.4 Hz, 1H), 5.29 (s, 1H), 5.56 (s, 1H), 7.02–7.13 (m, 2H), 7.23–7.31 (m, 2H); ^{13}C NMR δ 15.7, 19.7, 31.4, 78.4, 115.6 (d, J = 23.0 Hz), 116.2, 124.0, 128.5 (d, J = 14.9 Hz), 129.0 (d, J = 8.4 Hz), 130.5 (d, J = 4.0 Hz), 146.8, 159.7 (d, J = 244.7 Hz). Anal. Calcd for $C_{12}H_{15}FO$: C, 74.20; H, 7.78. Found: C, 74.10; H, 8.11.

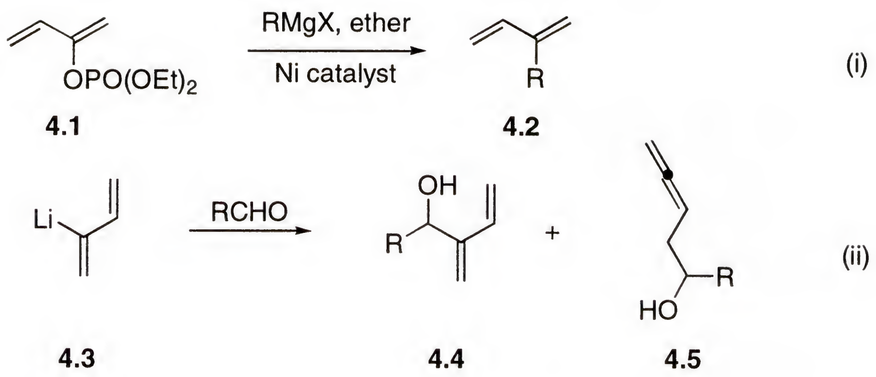
1-Cyclohexyl-2-(2-fluorophenyl)prop-2-en-1-ol (3.11l): Colorless oil (93% yield); ^{1}H NMR δ 0.96 –1.24 (m, 4H), 1.31–1.40 (m, 1H), 1.63–1.82 (m, 6H), 4.37 (d, J = 4.0 Hz, 1H), 5.30 (s, 1H), 5.54 (s, 1H), 7.03–7.15 (m, 2H), 7.25–7.31 (m, 2H); ^{13}C NMR δ 26.0, 26.3, 26.4, 26.6, 30.1, 41.4, 78.3 (d, J = 2.5 Hz), 115.6 (d, J = 22.9 Hz), 116.5, 124.0 (d, J = 3.4 Hz), 128.5 (d, J = 15.3 Hz), 129.0 (d, J = 8.5 Hz), 130.5 (d, J = 4.1 Hz), 146.5, 159.7 (d, J = 244.4 Hz). Anal. Calcd for $C_{17}H_{18}FO$: C, 76.89; H, 8.17. Found: C, 76.52; H, 8.49.

CHAPTER 4
PETERSON TYPE REACTIONS: A FOUR-CARBON UNIT REAGENT AS MASKED 1,3-DIENES

4.1 Introduction

Numerous studies have been performed on the regiospecific syntheses of 2-substituted 1,3-butadienes [94JOC4162] due to their use in the Diels-Alder reaction [92JCS(CC)953, 97JA7402] for the construction of complex molecules. Recent examples such as the synthesis of quartromicins by Roush and Barda [97TL8781], the synthesis of Bacatin III-steroid hybrid by Alaimo *et al* [94TL6603] and (±)-Ipsenol by Najera and Sansano [93TL3781] demonstrated the enormous potential of such an approach.

The literature methods for the syntheses of 2-alkyl-substituted 1,3-dienes can be divided into two categories. The first one uses preformed 1,3-butadien-2-yl reagents (Scheme 4.1) which were prepared (i) by nickel (II) catalyzed coupling of diethyl 1-methylene-2-propenyl phosphates **4.1** with Grignard reagents [83TL5137] or (ii) from 2-lithio-1,3-butadiene **4.3** synthesized *via* a Shapiro reaction [82TL3733] or by lithium-halogen exchange upon 2-chloro-1,3-butadiene [94JOC4162, 87BCJ325, 92TL6147]. In principle the use of preformed 1,3-butadien-2-yl reagents is a good strategy for the synthesis of 2-alkyl-substituted 1,3-dienes, but in many cases the requisite starting materials were not readily available and frequently allenes such as **4.5** were formed as unwanted by-products [94JOC4162, 87BCJ325, 92TL6147].



Scheme 4.1

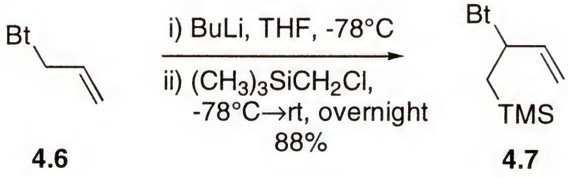
The second category of pathways to 2-alkyl-substituted 1,3-butadienes builds the backbone of the diene with a variety of different multistep approaches: (i) synthesis using boronate reagents developed by Soundararajan, Li and Brown [95TL2441, 96JOC100] synthesis using trimethylsilyl reagents developed by Hatakeyama *et al* [91TL4509, 91TL4513] or synthesis using diethyl phosphate esters [84T3645]; (ii) synthesis using propargylic ethers [96TL7275]; (iii) addition of bromomethanesulfonyl bromide to 2-substituted propenes followed by a Ramberg-Bäcklund elimination of sulfur dioxide and hydrogen bromide [84TL5469, 86JA4568]; (iv) transition metal-catalyzed methods including β-vinylation of α-olefins catalyzed by Ni and Zr [95MI113], and palladium-catalyzed 1,2-elimination of methylvinylcarbinol acetates [84TL5193]; (v) silicon [94TL6603, 93TL3781, 87TL693, 90HCA353, 91JCS(P1)1893] and tin [81TL2675] directed synthesis of dienes.

It was recently shown that easily accessible 2-benzotriazolylethylsilanes undergo vicinal elimination of silicon and the benzotriazole residue under various conditions to afford ethylenes [97JA9321]. We now describe the use of 1-{1-[(trimethylsilyl)-

methyl]prop-2-enyl}-1*H*-benzotriazole (**4.7**) (Scheme 4.2) as a four–carbon unit for the regiospecific synthesis of 2-alkyl-substituted 1,3-butadienes.

4.2 Results and Discussion

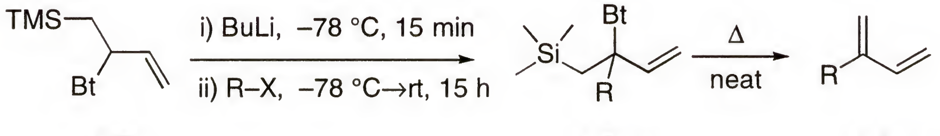
Reagent **4.6** was prepared from allyl bromide and benzotriazole in a multi-gram-scale by a literature method [92LA843]. Lithiation of **4.6** was accomplished with BuLi in dry THF at –78 °C for 30 min. The subsequent addition of chloromethyltrimethylsilane provided 1-{1-[(trimethylsilyl)methyl]prop-2-enyl}-1*H*-benzotriazole (**4.7**) as a colorless stable oil in 88% yield.



Scheme 4.2

Compound **4.7** was further deprotonated with BuLi and the resulting carbanion was alkylated with alkyl halides to give the intermediates **4.8a-e** (Scheme 4.3) in excellent yields without the formation of unwanted side products such as allenes [94JOC4162, 87BCJ325, 92TL6147]. Pyrolysis of the intermediates **4.8** (neat, 75–135 °C, 6–8 h) led to the elimination of *N*-trimethylsilyl benzotriazole providing the desired dienes **4.9**. These could be isolated in good yields in the case of the dienes **4.9a-c** (Scheme 4.3). On the other hand, the dienes **4.9d-e** polymerized under the reaction conditions used. However, we were able to trap them *in situ* as Diels-Alder-adducts

(**4.10a** and **4.10b**; 65 % and 54 % yield from **4.6**) by heating their precursors **4.8d** and **4.8e** in the presence of an appropriate dienophile (Scheme 4.4). Hence, the isolation of the dienes is not required if they are intended as dienophiles in Diels-Alder reactions.

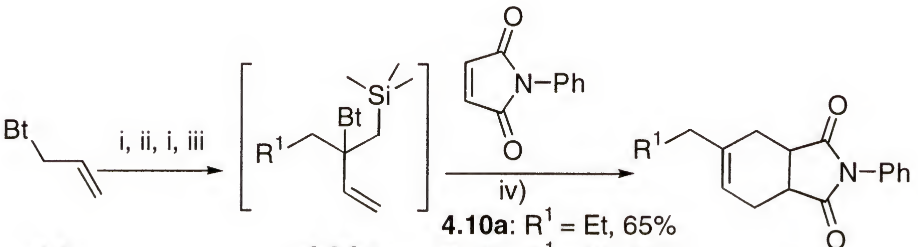


4.7 **4.8a-e** **4.9a-c**

	R–X	Elimination conditions temp (°C)	time (h)	Yield (%)[b] 4.8	4.9
a	$C_6H_{13}Br$	120-130	7	82	70
b	$C_{10}H_{21}Cl$	120-125	6	90	64
c	$C_{12}H_{25}Br$	130-135	8	86	90
d	C_3H_7I	25	2	87	[a]
e	$PhCH_2Br$	75-80	6	85	[a]

[a] See Scheme 4.4. [b] Compounds **4.8b,c**, **4.9c** were made by Dr. Larisa Serdyuk.

Scheme 4.3



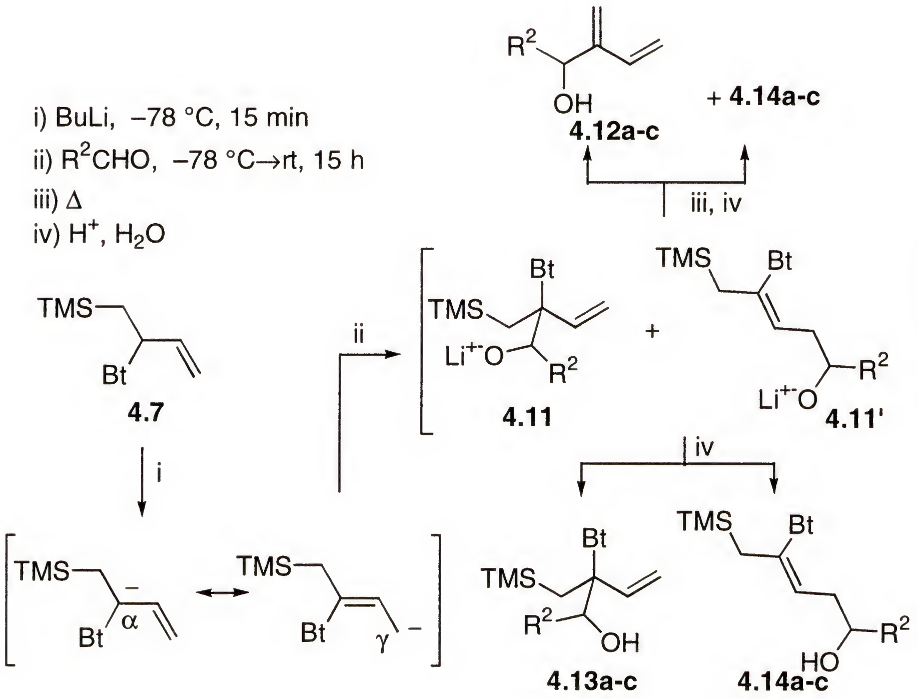
4.10a: R^1 = Et, 65%
4.10b: R^1 = Ph, 54%

4.6 **4.8d,e** **4.10a,b**

Reaction conditions[a]: i) BuLi, −78 °C, 30 min; ii) $(CH_3)_3SiCH_2Cl$, −78 °C→rt; iii) R^1CH_2Br, −78 °C→rt; iv) (**4.10a**), TFA, 25 °C, 2 h; (**4.10b**), neat, 75–80 °C, 6 h. [a] Compound **4.10b** was made by Dr. Larisa Serdyuk.

Scheme 4.4

Deprotonation of compound **4.7** with BuLi and addition of aliphatic aldehydes followed by aqueous work-up provided the homoallylic alcohols **4.13** as diastereomeric mixtures (Scheme 4.5). It should be noted that aldehydes do not always attack the α-position of the carbanion resulting from the deprotonation of **4.7** exclusively (to provide the intermediates **4.11**) but also its γ-position (to provide the intermediates **4.11'**). Therefore, in two cases, presumably due to the relatively great sterical demand of the aldehydes used, the formation of the regioisomeric homoallylic alcohols **4.14** (Scheme 4.5) as by-products was observed (**4.13b** : **4.14b** = 87 : 13; **4.13c** : **4.14c** = 91 : 9 according to GC-MS).



		Elimination conditions		Yield (%)^c	
	R^2CHO	temp (°C)	time (h)	**4.12**	**4.13**
a	$PhCH_2CH_2CHO$	56	3	74^a	80
b	$PhCH(CH_3)CHO$	56	5	60^a	75^b
c	$CH_3CH(CH_3)CHO$	56	5	72	74^b

[a] Yield based on one pot reaction from **4.6**. [b] Not separated, yield based on GC-MS of crude product [c] Compounds **4.12a**, **4.13a** were made by Dr. Larisa Serdyuk

Scheme 4.5

Heating the intermediates **4.11** and **4.11'** prior to the aqueous work-up furnished the dienes **4.12a-c** in good yields (together with small amounts of the homoallylic alcohols **4.14**). This outcome is the result of a [1,4]-C→O silicon migration and concerted elimination of the benzotriazolate moiety, followed by hydrolysis of the intermediate silyl ethers.

In conclusion, the convenient and regiospecific synthesis of masked 2-substituted butadienes has been developed. The regiochemistry of the reaction **4.7→4.8** or **4.7→4.11** is dependent upon the nature of the electrophile. The advantages of this methodology over the previously described methods include its high regioselectivity, easily available precursors and stable masked butadienes.

4.3 Experimental Section

NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) and $CDCl_3$ as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon atmosphere. All reagents were used as purchased from commercial suppliers without further purification.

4.3.1 Preparation of 1-[(Trimethylsilyl)methyl]prop-2-enyl-1*H*-1,2,3-benzotriazole (4.7).

To a solution of **4.6** (5 mmol) in THF (50 mL) at –78 °C under argon was added *n*-BuLi (1.52 M, 3.7 mL, 5.2 mmol). After stirring for 30 min, a solution of chloromethyltrimethylsilane (0.73 mL, 5.2 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to rt overnight before being washed with water (2

× 20 mL), and extracted with ethyl ether (2 × 20 mL). The combined ethereal phases were dried with Na_2SO_4 before removing the solvent *in vacuo*. The residue was subjected to column chromatography with hexanes : ethyl acetate = 20 : 1 to give the pure product as a colorless oil (1.08 g, 88%): ^{1}H NMR δ –0.13 (s, 9H), 1.52 (dd, J = 14.6, 7.1 Hz, 1H), 1.70 (dd, J = 14.8, 8.8 Hz, 1H), 5.15 (d, J = 9.0 Hz, 1H), 5.20 (s, 1H), 5.51 (q, J = 7.5 Hz, 1H), 6.09–6.20 (m, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ –1.5, 22.2, 59.9, 110.2, 116.7, 120.0, 123.7, 126.8, 131.9, 138.0, 146.4. Anal. Calcd for $C_{13}H_{19}N_3Si$: C, 63.63; H, 7.80; N, 17.12. Found: C, 63.37; H, 8.15; N, 17.42.

4.3.2 General Procedure for the Synthesis of Compounds 4.8a–e.

To a solution of **4.7** (0.98 g, 4 mmol) in THF (50 mL) at –78 °C under argon was added *n*-BuLi (1.52 M, 2.9 mL, 4.1 mmol). After stirring for 15 min a solution of the appropriate alkyl halide (4.1 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to rt overnight, before being washed with water (2 × 20 mL), extracted with ethyl ether (2 × 20 mL). The combined ethereal phases were dried with Na_2SO_4 before removing the solvent *in vacuo*. The residue was subjected to column chromatography with hexanes : ethyl acetate = 8 : 1 to give the pure product.

1-{1-Hexyl-1-[(trimethylsilyl)methyl]prop-2-enyl}-1*H*-1,2,3-benzotriazole (4.8a): Colorless oil (1.00 g, 82%): ^{1}H NMR δ –0.26 (s, 9H), 0.72 (t, J = 6.8 Hz, 3H), 1.09–1.20 (m, 8H), 1.70 (d, J = 14.8 Hz, 1H), 1.79 (d, J = 14.9 Hz, 1H), 2.18–2.38 (m, 2H), 5.16 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 11.0 Hz, 1H), 6.12 (dd, J = 17.6, 10.8 Hz, 1H), 7.18–7.29 (m, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ –0.1, 13.9, 22.4, 23.5, 26.9, 29.2, 31.5, 39.2, 69.1, 112.7, 115.1, 119.9, 123.3, 126.1, 132.3, 142.2, 147.0. Anal. Calcd for $C_{19}H_{31}N_3Si$: C, 69.24; H, 9.50; N, 12.75. Found: C, 68.92; H, 9.75; N, 12.71.

1-{1-Decyl-1-[(trimethylsilyl)methyl]prop-2-enyl}-1*H*-1,2,3-benzotriazole (4.8b): Colorless oil (1.39 g, 90%): ^{1}H NMR δ –0.18 (s, 9H), 0.84 (t, *J* = 5.7 Hz, 3H), 1.12–1.28 (m, 16H), 1.78 (d, *J* = 14.9 Hz, 1H), 1.87 (d, *J* = 14.9 Hz, 1H), 2.25–2.42 (m, 2H), 5.24 (d, *J* = 17.4 Hz, 1H), 5.35 (d, *J* = 10.7 Hz, 1H), 6.20 (dd, *J* = 17.4, 10.7 Hz, 1H), 7.26–7.36 (m, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ –0.1, 14.0, 22.6, 23.5, 26.9, 29.2, 29.3, 29.4, 29.6, 29.7, 31.8, 39.2, 69.1, 112.7, 115.0, 120.0, 123.3, 126.1, 132.3, 142.3, 147.0. Anal. Calcd for $C_{23}H_{39}N_3Si$: C, 71.63; H, 10.19; N, 10.90. Found: C, 71.95; H, 10.47; N, 10.66.

1-{1-Dodecyl-1-[(trimethylsilyl)methyl]prop-2-enyl}-1*H*-1,2,3-benzotriazole (4.8c): Colorless oil (1.33 g, 86%): ^{1}H NMR δ –0.16 (s, 9H), 0.87 (t, *J* = 6.1 Hz, 3H), 1.18–1.27 (m, 20H), 1.80 (d, *J* = 14.9 Hz, 1H), 1.89 (d, *J* = 14.9 Hz, 1H), 2.26–2.44 (m, 2H), 5.26 (d, *J* = 17.5 Hz, 1H), 5.38 (d, *J* = 10.8 Hz, 1H), 6.22 (dd, *J* = 17.5, 10.8 Hz, 1H), 7.30 (t, *J* = 6.6 Hz, 1H), 7.36 (t, *J* = 6.6 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ –0.1, 14.1, 22.6, 23.5, 26.9, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 39.2, 69.1, 112.7, 115.0, 120.0, 123.3, 126.1, 132.3, 142.2, 147.0. Anal. Calcd for $C_{25}H_{43}N_3Si$: N, 10.16. Found: N, 10.32.

1-{1-Propyl-1-[(trimethylsilyl)methyl]prop-2-enyl}-1*H*-1,2,3-benzotriazole (4.8d): Colorless oil (1.50 g, 87%): ^{1}H NMR δ –0.10 (s, 9H), 0.91 (t, *J* = 6.9 Hz, 3H), 0.97–1.05 (m, 1H), 1.33-1.43 (m, 1H), 1.87 (d, *J* = 14.8 Hz, 1H), 1.96 (d, *J* = 14.5 Hz, 1H), 2.31–2.52 (m, 2H), 5.33 (d, *J* = 17.6 Hz, 1H), 5.44 (d, *J* = 10.7 Hz, 1H), 6.28 (dd, *J* = 17.6, 10.7 Hz, 1H), 7.35–7.45 (m, 2H), 7.68 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ –0.2 (3C), 13.9, 16.8, 26.8, 41.3, 69.0, 112.7, 115.0, 119.9, 123.3, 126.1, 132.3, 142.1, 146.9. Anal. Calcd for $C_{16}H_{25}N_3Si$: C, 66.84; H, 8.78. Found: C, 66.62; H, 8.59.

1-{1-Benzyl-1-[(trimethylsilyl)methyl]prop-2-enyl}-1*H*-1,2,3-benzotriazole (4.8e): Colorless oil (2.90 g, 85%): ^{1}H NMR δ –0.11 (s, 9H), 1.62 (d, *J* = 14.6 Hz, 1H), 2.06 (d, *J* = 14.6 Hz, 1H), 3.59 (s, 2H), 5.36 (d, *J* = 17.6 Hz, 1H), 5.47 (d, *J* = 10.9 Hz, 1H), 6.35 (dd, *J* = 10.9, 17.5 Hz, 1H), 6.61 (d, *J* = 7.3 Hz, 1H), 7.00–7.20 (m, 3H), 7.32–7.40 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ 0.3, 27.6, 46.0, 69.1, 112.7, 115.7, 120.0, 123.4, 126.3, 126.8, 127.8, 130.4, 132.7, 135.3, 141.5, 146.9. HRMS (M + 1, FAB) calcd for $C_{20}H_{26}N_3Si$: 336.1896 (M + 1). Found: 336.1898.

4.3.3 General Procedure for the Synthesis of Compounds 4.9a–c.

The corresponding compound **4.8a-c** (2 mmol) was stirred at 130–135 °C under argon for 8-12 h. The cold reaction mixture was dissolved in diethyl ether (40 mL) and washed with NaOH solution (10%, 2 × 20 mL) and water (2 × 20 mL). The ethereal phase was dried with Na_2SO_4 before removing the solvent *in vacuo*. The residue was subjected to column chromatography with hexanes : ethyl acetate = 40 : 1 to afford the pure product.

2-Hexylbuta-1,3-diene (4.9a): Colorless oil (lit [95RCB113] oil) (0.20 g, 70%): ^{1}H NMR δ 0.93 (t, *J* = 6.9 Hz, 3H), 1.20–1.45 (m, 6H), 1.45–1.60 (m, 2H), 2.24 (t, *J* = 8.0 Hz, 2H), 5.02–5.03 (m, 2H), 5.07 (d, *J* = 10.9 Hz, 1H), 5.26 (d, *J* = 17.6 Hz, 1H), 6.40 (dd, *J* = 17.6, 10.7 Hz, 1H); ^{13}C NMR δ 14.1, 22.7, 28.2, 29.3, 31.4, 31.8, 113.0, 115.4, 139.1, 146.7.

2-Decylbuta-1,3-diene (4.9b): Colorless oil (0.32 g, 64%): ^{1}H NMR δ 0.91 (t, J = 6.8 Hz, 3H), 1.20–1.40 (m, 14H), 1.49–1.54 (m, 2H), 2.22 (t, J = 8.0 Hz, 2H), 5.01–5.02 (m, 2H), 5.07 (d, J = 10.8 Hz, 1H), 5.25 (d, J = 17.6 Hz, 1H), 6.40 (dd, J = 17.6, 10.7 Hz, 1H); ^{13}C NMR δ 14.1, 22.7, 28.2, 29.4, 29.6, 29.7, 31.4, 32.0, 113.0, 115.4, 139.1, 146.7; HRMS calcd for $C_{14}H_{26}$: 194.2035. Found: 194.2013 (EI).

2-Dodecylbuta-1,3-diene (4.9c): Colorless oil (0.40 g, 90%): ^{1}H NMR δ 0.91 (t, J = 6.5 Hz, 3H), 1.20–1.35 (m, 18H), 1.46–1.53 (m, 2H), 2.22 (t, J = 7.6 Hz, 1H), 5.00–5.02 (m, 2H), 5.07 (d, J = 10.8 Hz, 1H), 5.25 (d, J = 17.6 Hz, 1H), 6.40 (dd, J = 17.6, 10.8 Hz, 1H); ^{13}C NMR δ 14.1, 22.7, 28.2, 29.4, 29.6, 29.7, 31.4, 32.0, 113.0, 115.4, 139.1, 146.7; HRMS (EI) calcd for $C_{16}H_{30}$: 222.2348. Found: 222.2351.

4.3.4 General Procedure for the Synthesis of Compounds 4.10a,b.

n-BuLi in hexane (1.4 M, 3.7 mL, 5.1 mmol) was added to a solution of **4.6** (0.80 g, 5 mmol) in THF (50 mL) at –78 °C. After stirring for 30 min at –78 °C, a solution of chloromethyltrimethylsilane (0.63 g, 5.1 mmol) in THF (5 mL) was added, and the reaction mixture was allowed to warm to rt overnight. The reaction mixture was cooled to –78 °C and BuLi in hexane (1.4 M, 3.6 mL, 5.0 mmol) was added. After 15 min a solution of 1-iodopropane (0.48 mL, 5.0 mmol), in the case of **4.10a**, or benzyl bromide (0.86 g, 5.0 mmol) in THF (5 mL), in the case of **4.10b**, was added. After the reaction reached rt overnight, the mixture was washed with water (2 × 20 mL), extracted with diethyl ether (2 × 20 mL). The combined ethereal phases were dried with Na_2SO_4 before removing the solvent *in vacuo*. The residue (crude **4.8d**) was purified as previously described and was used for the synthesis of **4.10a**. The crude product **4.8e** was used without further purification for the synthesis of **4.10b**. In the case of **4.10a**, *N*-

phenylmaleinimide was added (0.45 g, 2.6 mmol) to a solution of **4.8d** (0.50 g, 1.7 mmol) in methylene chloride (30 mL) followed by slow addition of trifluoroacetic acid (0.8 mL, 10 mmol). After two hours stirring at rt the mixture was washed with aqueous sodium hydroxide solution (0.5 M, 20 mL), and dried (Na_2SO_4) before removing the solvent. In the case of **4.10b**, *N*-phenylmaleinimide was added (1.04 g, 6.0 mmol) to the ether solution, and the mixture was heated under reflux for 1 h. The solvent was removed by distillation under a stream of nitrogen and the remaining oil was heated at 75–80 °C for 6 h. After the reaction mixture was cooled down to rt, it was dissolved in diethyl ether (40 mL), washed with aqueous sodium carbonate (10%, 40 mL) and water (40 mL). The ethereal phase was dried with Na_2SO_4 before removing the solvent *in vacuo*. The residue was subjected to column chromatography with hexanes : ethyl acetate = 2:1 to give the pure product.

2-Phenyl-5-propyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (4.10a): Colorless oil (0.40 g, 65%): ^{1}H NMR δ 0.86 (t, J = 7.1 Hz, 3H), 1.25–1.48(m, 2H), 2.02 (t, J = 7.4 Hz, 2H), 2.25–2.32 (m, 2H), 2.61–2.74 (m, 2H), 3.20–3.30 (m, 2H), 5.58-5.70 (m, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.36–7.49 (m, 3H); ^{13}C NMR δ 13.7, 20.4, 24.3, 27.6, 39.2, 39.4, 39.7, 119.9, 126.3, 128.4, 129.0, 132.0, 140.6, 179.1, 179.3. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.12; N, 5.20. Found: C, 75.46; H, 7.24; N, 5.42.

2-Phenyl-5-(phenylmethyl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (4.10b): Yellow oil (0.86 g, 54%): ^{1}H NMR δ 2.22–2.34 (m, 2H), 2.58 (d, J = 15.5 Hz, 1H), 2.69 (dd, J = 15.5, 6.6 Hz, 1H), 3.15–3.20 (m, 2H), 3.34 (s, 2H), 5.62–5.66 (m, 1H), 7.09–7.26 (m, 6H), 7.34–7.46 (m, 4H); ^{13}C NMR δ 24.4, 27.6, 39.3, 39.6, 43.7, 121.6, 126.3, 128.4, 128.9, 129.0, 132.0, 138.5, 139.9, 178.7, 179.1. HRMS calcd for $C_{21}H_{19}NO_2$: 318.1494 (M+1). Found: 318.1497 (M+1, FAB).

4.3.5 General Procedure for the Synthesis of Compounds 4.13a and 4.14c.

To a solution of **4.7** (0.98 g, 4 mmol) in THF (50 mL) at –78 °C under argon was added BuLi (1.52 M in hexane, 2.9 mL, 4.1 mmol). After stirring for 15 min a solution of the corresponding aldehyde (4.1 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to rt overnight before being washed with water (2 × 20 mL), and extracted with diethyl ether (2 × 20 mL). The combined ethereal phases were dried with Na_2SO_4 before removing the solvent *in vacuo*. The residue was subjected to column chromatography to give the pure product.

4-(1*H*-1,2,3-Benzotriazol-1-yl)-1-phenyl-4-[(trimethylsilyl)methyl]hex-5-en-3-ol (4.13a): Yellow oil (1.52 g, 80%), 1.3:1 mixture of diastereomers (minor diastereomer in square brackets): ^{1}H NMR δ –0.10 (s, 9H) [–0.24 (s, 9H)], 1.71–2.21 (m, 4+[4]H), 2.85–2.95 (m, 2H) [3.15–3.30 (m, 2H)], 4.08 (s, 1H) [4.09 (s, 1H)], 4.74–4.79 (m, 1H) [5.10–5.13 (m, 1H)], 5.36 (d, J = 18.0 Hz, 1H) [5.53 (d, J = 18.0 Hz, 1H)], 5.58 (d, J = 11.4 Hz, 1H) [5.70 (d, J = 11.4 Hz, 1H)], 6.32 (dd, J = 17.5, 10.8 Hz, 1H) [6.55 (dd, J = 17.5, 10.8 Hz, 1H)], 7.34–7.58 (m, 7+[7]H), 7.77 (d, J = 7.8 Hz, 1H) [7.78 (d, J = 7.8 Hz, 1H)], 8.22 (d, J = 7.8 Hz, 1+[1]H); ^{13}C NMR δ –0.1 [–0.8], 22.5 [23.0], 32.5 [32.4], 33.0 [32.9], 73.4 [73.2], 75.6 [73.7], 113.1 [112.8], 117.3 [117.6], 119.9, 123.7 [123.8], 125.7 [125.8], 126.7 [126.9], 128.2 [128.3], 128.4 [128.5], 132.6 [132.7], 139.5 [138.2], 141.7 [141.9], 146.2 [146.4]. HRMS calcd for $C_{25}H_{43}N_3Si$: 380.2158 (M+1). Found: 380.2144 (M+1, FAB).

6-(1*H*-1,2,3-Benzotriazol-1-yl)-6-[(trimethylsilyl)methyl]-2-methylhex-5-en-3-ol (4.14c): Hexanes : EtOAc = 8 : 1; yellow oil (0.34 g, 22%): ^{1}H NMR δ –0.20 (s, 9H), 1.01 (d, J = 6.7 Hz, 6H), 1.75–1.85 (m, 1H), 2.39–2.51 (m, 2H), 2.46 (s, 2H), 3.55–3.60 (m, 1H), 5.87 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ –1.5 (3C), 17.4, 18.8, 21.3, 32.7, 33.5, 76.3, 111.0, 118.5, 120.0, 124.0, 127.6, 132.2, 136.4, 146.0. Anal. Calcd for $C_{17}H_{27}N_3OSi$: N, 13.24. Found: N, 13.35.

4.3.6 General Procedure for the Synthesis of Compounds 4.12a–c.

To a solution of **4.7** (0.98 g, 4 mmol) in THF (50 mL) at –78 °C under argon was added *n*-BuLi (1.52 M, 2.9 mL, 4.1 mmol). After stirring for 15 min a solution of the appropriate aldehyde (4.1 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to rt overnight and then refluxed in THF under argon for 3 h. The reaction mixture was allowed to cool down to rt and was washed with saturated aqueous ammonium chloride solution (40 mL), HCl (10%, 2 × 20 mL) and water (2 × 20 mL) before being extracted with diethyl ether (2 × 20 mL). The combined ethereal phases were dried with Na_2SO_4 before removing the solvent *in vacuo*. The residue was subjected to column chromatography to give the pure product.

4-Methylidene-1-phenylhex-5-en-3-ol (4.12a): Yellow oil (lit [91TL4509] oil), (0.69 g, 74%): ^{1}H NMR δ 1.80–2.02 (m, 3H), 2.67–2.83 (m, 2H), 4.41 (dd, J = 7.3, 3.8 Hz, 1H), 5.05 (d, J = 11.3 Hz, 1H), 5.15 (s, 1H), 5.20 (d, J = 18.0 Hz, 1H), 5.26 (s, 1H), 6.32 (dd, J = 18.0, 11.3 Hz, 1H), 7.15–7.30 (m, 5H); ^{13}C NMR δ 32.0, 37.9, 70.6, 114.1, 114.3, 125.8, 128.3, 128.5, 136.1, 141.9, 149.1.

3-Methylidene-1,1-methylphenylpent-4-en-2-ol (4.12b): Yellow oil, (0.45 g, 60%): ^{1}H NMR δ 1.23 (d, *J* = 7.1 Hz, 3H), 1.79 (s, 1H), 3.02–3.11 (m, 1H), 4.51 (d, *J* = 4.4 Hz, 1H), 5.09 (d, *J* = 11.0 Hz, 1H), 5.16 (s, 1H), 5.20 (s, 1H), 5.33 (d, *J* = 17.6 Hz, 1H), 6.31 (dd, *J* = 17.9, 11.3 Hz, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR δ 13.6, 42.9, 75.3, 114.1, 115.3, 126.3, 127.7, 128.3, 136.4, 144.5, 147.0. Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.58. Found: C, 82.61; H, 8.48.

2-Methyl-4-methylidenehex-5-en-3-ol (4.12c): Yellow oil (lit [94JOC4162] oil) , (0.56 g, 72%):^{1}H NMR δ 0.93 (d, *J* = 6.6 Hz, 6H), 1.72 (br s, 1H), 1.80-2.00 (m, 1H), 4.12 (d, *J* = 5.8 Hz, 1H), 5.10 (d, *J* = 11.1 Hz, 1H), 5.17 (s, 1H), 5.20 (s, 1H), 5.36 (d, *J* = 17.9 Hz, 1H), 6.33 (dd, *J* = 11.0, 17.6 Hz, 1H); ^{13}C NMR δ 16.9, 19.6, 32.0, 77.2, 114.4, 114.6, 136.2, 148.3.

CHAPTER 5

[3+2] CYCLOADDITIONS, PART I: A FACILE SYNTHESIS OF 3-FUNCTIONALIZED-2-AMINOTHIOPHENES AND 1,3-DISUBSTITUTED-2-SULFANYLPYRROLES

5.1 Introduction

Cycloadditions are powerful synthetic tools [98JCS(P1)3873]. Recently, novel routes to important heterocycles, including 2-aminothiophenes and 2-alkylthiopyrroles, were opened by [3+2] cycloadditions of unsaturated carbanions with isothiocyanates [99JHC1469].

Since the first report on the preparation of 2-aminothiophene [1885CB1490], the synthesis of functionalized aminothiophenes has been studied extensively [86MI631]. Four main synthetic approaches have been applied, most of which are modifying already existing thiophene rings: (i) reduction of nitro- [33LA174] or nitroso-thiophenes [70KG1624], (ii) Beckmann, Schmidt [51JA613] or Curtius rearrangements [81JHC851] of thiophenecarboxylic acid derivatives, and (iii) nucleophilic displacements of mercapto- [69JPR827] or iodo-thiophenes [74JCS(CC)256] with amines. Route (iv), ring closure reactions from non thiophene based starting materials, are less developed for the preparation of simple 2-aminothiophenes. To the best of our knowledge the only described examples are based on the use of (a) methyl *N*-phenyl-2-alkenimidothioates [85S172], (b) metallic ynamines or allenic amines [98TL2433, 86JOMC21], and (c) lithiated 1-alkynes or allenes [98MI253].

The synthesis for 3-substituted-2-(alkylthio)pyrroles, especially those with an electron-donating 3-substituent, are rather limited. The two main synthetic routes are (i) [3+2] cycloadditions of acyl or nitroketene *S,N*-acetals with bromoacetaldehyde acetal [76JCS(CC)593, 89S141]. These reactions proceed highly regioselectively but provide only products with an electron-withdrawing substituent (acyl or nitro) at the C(3) position. (ii) [3+2] cycloadditions of 1-lithiomethoxyallene with cyclohexylisothiocyanate or methylisothiocyanate gave 2-ethylthio-3-methoxy-*N*-cyclohexylpyrrole or 2-methylthio-3-methoxy-*N*-methylpyrrole in 11% or 54% yield respectively [96CHC781, 97MI76].

Benzotriazole-stabilized carbanions have already been used successfully for the preparation of pyrroles [95TL343] and furans [95S1315]. Our goal was to investigate their utility for the synthesis of 3-functionalized-2-aminothiophenes and 1,3-disubstituted-2-methylthiopyrroles *via* [3+2] cycloaddition.

5.2 Results and Discussion

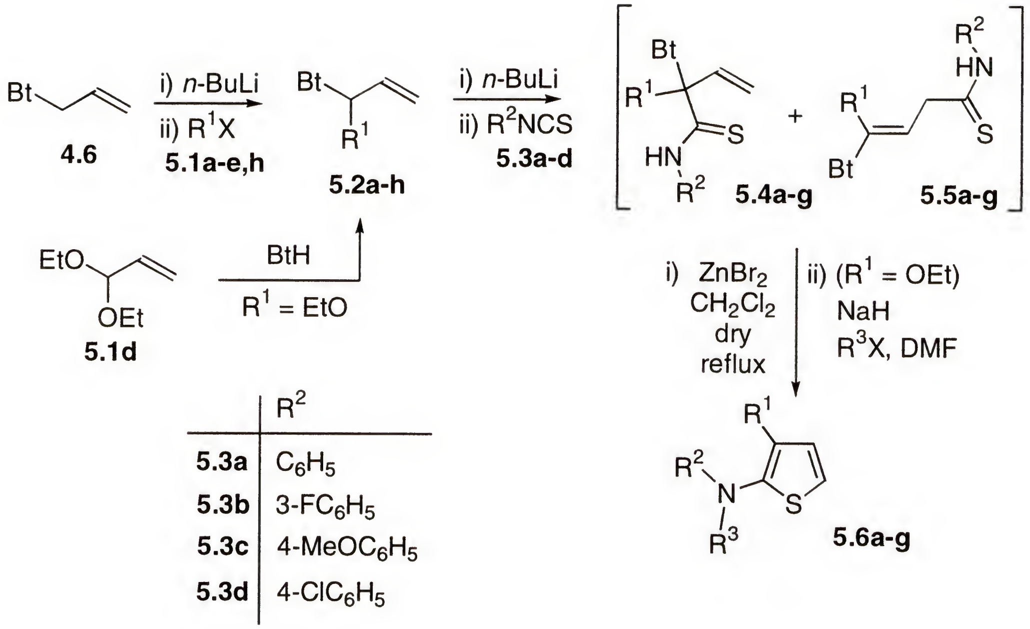
5.2.1. Synthesis of 3-Substituted-2-aminothiophenes.

1-Propen-2-ylbenzotriazole (**4.6**) was deprotonated with a hexane solution of *n*-BuLi at –78 °C (prevents the isomerization of compound **4.6** [92LA843]) and alkylated subsequently with various electrophiles **5.1a-c,e-f** [92LA843] to give 1-alkylpropen-2-ylbenzotriazoles **5.2a-c,e-f** (Table 5.1) in good yields. 1-Allyl benzotriazole **5.2d** was obtained by heating acrolein diethyl acetal **5.1d** with benzotriazole in hexane (replacing performance fluid in the literature [95JOC7589]) under reflux for 18 h, followed by purification with flush column chromatography to separate Bt[1] and Bt[2] isomers.

Table 5.1. Preparation of 1-Substituted propen-2-ylbenzotriazoles **5.2a-h**.

	5.1	yield (%) of **5.2**
a	n-$C_6H_{13}Br$	82
b	EtI	80
c	2-$ClC_6H_4CH_2Cl$	98
d	$(EtO)_2CHCH{=}CH_2$	88[a]
e	$CH_2{=}CHCH_2Cl$	70
f	2-$FC_6H_4CH_2Cl$	75
g	n-C_3H_7I	55
h	n-$C_8H_{17}Cl$	77

Deprotonation of the benzotriazole derivatives **5.2a-f** with *n*-BuLi, followed by the addition of the isothiocyanates **5.3a-d** (see Scheme 5.1) at –78 °C gave the expected thioamides **5.4a-g** as the major products (accompanied by corresponding regioisomers **5.5a-c,e-g**). The reaction usually proceeds with low to moderate regioselectivity (Table 5.2). However, the reaction between the α-ethoxy derivative **5.2d** and phenyl isothiocyanate furnished exclusively the desired regioisomer **5.4d**. This can be explained by the stabilization of the α-carbanion due to the electron withdrawing effect of the nearby ethoxy group.



	R^2
5.3a	C_6H_5
5.3b	$3\text{-}FC_6H_5$
5.3c	$4\text{-}MeOC_6H_5$
5.3d	$4\text{-}ClC_6H_5$

[a] For the significance of **5.2a-h**, see Tabel 5.1; for the significance of **5.6a-g**, see Table 5.2.

Scheme 5.1

The regioisomeric mixtures of the thioamides **5.4** and **5.5** were used for the $ZnBr_2$ mediated synthesis of the desired 3-substituted-2-aminothiophenes **5.6** without further purification because they are prone to decomposition on column chromatography (however, **5.4a** could be isolated by recrystallization from Et_2O). It should be noted that the only the α-benzotriazolyl thioamides **5.4** were transformed to the corresponding 3-substituted-2-aminothiophenes **5.6**, while their regioisomers **5.5** remained unchanged. After removal of the benzotriazole by washing with aqueous sodium hydroxide solution and flash column chromatography the desired products **5.6** were obtained in 25–80% overall yield from **5.2**. Due to the relative instability of thienylamines [98MI253], we encountered some problems in getting correct elemental CHN analyses for **5.6f** and **5.6g**.

Table 5.2. Preparation of 3-Substituted-2-aminothiophenes **5.6a-g**.

	R^1	R^2	Crude **5.4** +**5. 5** yield(%)	Ratio **5.4**:**5.5**[a]	yield (%)[b] of **5.6**	Starting Materials
a	Et	C_6H_5	106	1.6 : 1	50[c]	**5.2b**, **5.3a**
b	2-ClC$_6$H$_4$CH$_2$	C_6H_5	112	6 : 1	80[c]	**5.2c**, **5.3a**
c	2-ClC$_6$H$_4$CH$_2$	3-FC$_6$H$_4$	102	5.8 : 1	69[c]	**5.2c**, **5.3b**
d	EtO	C_6H_5	118	∞	43[d]	**5.2d**, **5.3a**
e	*n*-C$_6$H$_{13}$	C_6H_5	111	1.7 : 1	41[c]	**5.2a**, **5.3a**
f	CH$_2$=CHCH$_2$	4-ClC$_6$H$_4$	102	1.3 : 1	25[c]	**5.2e**, **5.3d**
g	2-FC$_6$H$_4$CH$_2$	4-MeOC$_6$H$_4$	99	4 : 1	54[c]	**5.2f**, **5.3c**

[a] Determined from the crude product by ^{1}H NMR spectra; [b] Isolated yields of **5.6a-g** after chromatography based on **5.2a-f**; [c] R^3 = H; [d] R^3 = CH_3.

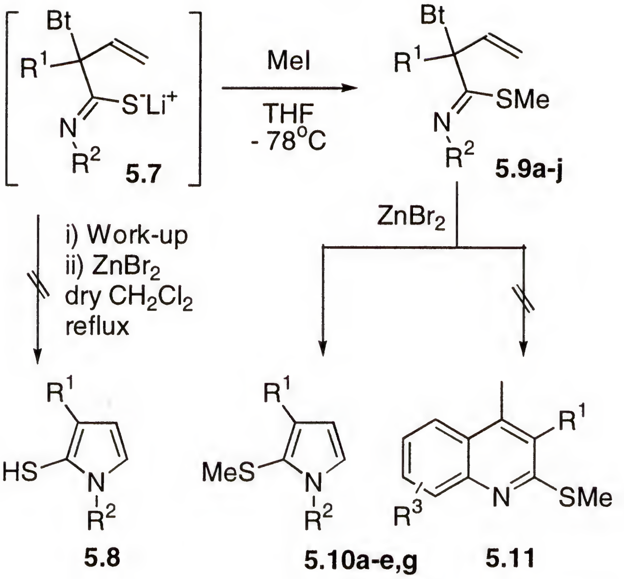
Thiophenes **5.6a-g** were substituted with different R^1 groups. Simple alkyl (in **5.6a,e**), benzyl (in **5.6b,c,g**), allyl (in **5.6f**) and ethoxy (in **5.6d**) groups were successfully utilized as substituents at the 3-position. Electron-withdrawing (in **5.3b,d**) and electron-donating (in **5.3c**) groups substituted phenyl isothiocyanates were also scanned in the generation of corresponding products **5.6c,f,g.** In these reactions the total yields were not greatly affected. The low regioselectivities in the case of **5.6a,e,f** are believed to be the effect of substituent R^1 group. As expected, final product **5.6g** is less stable than **5.6c** and **5.6f** due to the more electron-rich methoxy group. Since 3-alkoxythiophenes with primary or secondary amino group at the 2-position generally show low stability [99JHC1469], compound **5.6d** was isolated with 43% yield, after further quantitative *N*-methylation with methyl iodide.

5.2.2. Synthesis of 1,3-Disubstituted-2-methylsulfanylpyrroles

The cyclization reactions described in section 5.2.1 did not provide detectable amounts of the pyrroles **5.8** (Scheme 5.2). However, the 2-substituted-3-butenimidothioates **5.9** formed in moderate to good yields on *S*-methylation of the anions **5.7,** could be cyclized successfully in the presence of $ZnBr_2$ (Scheme 5.2) to give the 3-substituted-2-(methylsulfanyl)-1-aryl-1*H*-pyrroles **5.10**. During these cyclizations, no formation of quinolines **5.11** could be observed (Scheme 5.2).

The condensations between carbanion **5.2d** (R^1 = OEt) and the isothiocyanates **5.3**, followed by methylation of the resulting intermediates **5.7a-f** with MeI (attempts to replace MeI with benzoyl chloride or allyl chloride failed) provided exclusively the corresponding 2-substituted-3-butenimidothioates **5.9a-f**. The other regioisomers could not be detected by ^{1}H NMR spectroscopy (compared with the synthesis of **5.6d** described in 5.2.1). As in the analogous syntheses of the α-benzotriazolyl thioamides **5.4**, the regioselectivities were lower when R^1 were alkyl groups though corresponding regioisomers of **5.9** were not isolated.

The 3-substituted-2-(methylsulfanyl)-1-aryl-1*H*-pyrroles **5.10a-e** were readily obtained by refluxing a solution of the corresponding starting material **5.9** with $ZnBr_2$ in dry methylene chloride for 1 h (Table 5.3). The yields determined by GC on the crude mixtures were considerably higher than the isolated yields after column chromatography. This can be explained by the fact that electron-rich pyrroles are prone to decomposition. This might also be the reason why pyrrole **5.10f** (R^2 = 4-methoxyphenyl) which should result from cyclization of **5.9f** could neither be isolated nor detected by GC-MS.



[a]For the significance of **5.9** and **5.10**, see Table 5.3.

Scheme 5.2

Table 5.3. Synthesis[a] of Intermediates **5.9a-j** and Products **5.10a-g.**

	R^1	R^2	**5.9**		Cond.[c]	**5.10**	
			Y (%)[b]	mp (°C)		Y (%)[d]	Y (%)[e]
a	EtO	Ph	71	112.5-112.8	A	65	85
b	EtO	4-ClC_6H_4	63	78-79	A	33	76
c	EtO	4-FC_6H_4	59	78-81	A	38	94
d	EtO	3-FC_6H_4	60	113-115	A	59	79
e	EtO	2-ClC_6H_4	75	93-94	A	21	75
f	EtO	4-$CH_3OC_6H_4$	80	104-106	A	/	/
g	CH_2=$CHCH_2$	Ph	37	oil	B	33	79
h	*n*-C_3H_7	Ph	65	oil	A,B		
i	*n*-C_8H_{17}	Ph	75	oil	A,B		
j	2-$FC_6H_5CH_2$	Ph	73	oil	A,B		

[a]Compounds **5.9b-j**, **5.10b** were made by Ms. Anna Denisenko. [b]isolated yield based on **5.2**. [c]reaction condition of converting intermediates **5.9** to products **5.10**; A: $ZnBr_2$, dry CH_2Cl_2, reflux; B: $ZnBr_2$, dry toluene, reflux. [d]isolated yield based on **5.9;** [e]GC yield.

The cyclization of **5.9g** required harsher reaction conditions. Attempts to cyclize compound **5.9g** in dry methylene chloride as well as in 1,2-dichloroethane failed presumably because the allyl group is much less electron-donating than the methoxy group. Nevertheless, **5.9g** was successfully cyclized by refluxing in dry toluene ($ZnBr_2$, 1 d) to give the desired pyrrole **5.10g** (Table 5.3). However, attempts to cyclize the compounds **5.9h-j** analogously led only to the formation of complex reaction mixtures presumably because the resulting pyrroles **5.10h-j** decompose under these relatively harsh conditions. Currently, efforts are made to investigate milder and more efficient cyclization protocols.

In summary, our methodology provides a convenient pathway to the synthesis of novel 3-substituted-2-aminothiophenes **5.6** and 3-substituted-2-(methylsulfanyl)-1-aryl-1*H*-pyrroles **5.10** starting from easily accessible 1-propen-2-ylbenzotriazole. It complements known literature syntheses and usually provides the desired products in overall yields > 50% using mild reaction conditions.

5.3 Experimental Section

Melting points were determined with a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or $CDCl_3$ as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel (230-400 mesh).

5.3.1 General Procedure for the Preparation of 1-(1-Alkylprop-2-enyl)-1*H*-benzotriazoles 5.2a-c,e-h.

A solution of *n*-BuLi (1.47 M in hexane, 6.8 mL, 10.2 mmol) was added under argon atmosphere to a pre-chilled solution (–78 °C) of allylbenzotriazole (**4.6**) (1.59 g, 10 mmol) in dry THF (50 mL). After 20 min, the electrophile **5.1** (10.2 mmol) was added dropwise, and still at –78 °C the resulting mixture was stirred until complete conversion of the starting material (TLC control). A saturated aqueous solution of NH_4Cl (40 mL) was added, the mixture was allowed to warm up to rt and was subsequently extracted with Et_2O (3 × 30 mL) and the combined organic layers were dried (Na_2SO_4). Then the solvent was evaporated *in vacuo* and the resulting residue was purified by flash column chromatography on silica gel (pentane/Et_2O: 1/2) to give the desired **5.2** as pure products.

1-(1-Hexylprop-2-enyl)-1*H*-benzotriazole (5.2a): Colorless oil; ^{1}H NMR δ 0.82 (t, *J* = 6.9 Hz, 3H), 1.11–1.30 (m, 8H), 2.12–2.21 (m, 1H), 2.28–2.37 (m, 1H), 5.18 (d, *J* = 17.1 Hz, 1H), 5.29 (d, *J* = 16.9 Hz, 1H), 5.34–5.39 (m, 1H), 6.12–6.23 (m, 1H), 7.34 (t, *J* = 7.1 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 13.7, 22.2, 25.7, 28.4, 31.2, 33.3, 62.2, 109.9, 117.4, 119.7, 123.5, 126.7, 132.2, 135.7, 146.0. Anal. Calcd for $C_{15}H_{21}N_3$: H, 8.70; N, 17.27. Found: H, 8.90; N, 16.98.

1-(1-Ethylprop-2-enyl)-1*H*-benzotriazole (5.2b): Colorless oil; ^{1}H NMR δ 0.88 (t, *J* = 7.4 Hz, 3H), 2.16–2.39 (m, 2H), 5.17–5.28 (m, 3H), 6.12–6.23 (m, 1H), 7.34 (t, *J* = 7.1 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H);

^{13}C NMR δ 10.4, 26.7, 63.8, 109.9, 117.6, 119.8, 123.5, 126.7, 132.3, 135.5, 146.0. Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.33; H, 7.26; N, 22.89.

1-{1-[(2-Chlorophenyl)methyl]prop-2-enyl}-1*H*-benzotriazole (5.2c): Colorless oil; ^{1}H NMR δ 3.63–3.66 (m, 2H), 5.20 (d, *J* = 17.3 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 5.68 (d, *J* = 7.0, 7.6 Hz, 1H), 6.29–6.41 (m, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.27–7.36 (m, 4H), 8.00 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 38.5, 60.8, 109.3, 118.1, 119.6, 123.5, 126.6, 126.8, 128.3, 129.2, 131.4, 132.6, 133.7, 134.0, 134.9, 145.5. Anal. Calcd for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.96 H, 4.94; N, 14.90.

1-[(1-Vinyl)-3-butenyl]-1*H*-1,2,3-benzotriazole (5.2e): Colorless oil; ^{1}H NMR δ 2.90–2.99 (m, 1H), 3.04–3.14 (m, 1H), 4.98 (d, *J* = 10.2 Hz, 1H), 5.04 (d, *J* = 17.7 Hz, 1H), 5.19 (d, *J* = 16.8 Hz, 1H), 5.30 (d, *J* = 10.2 Hz, 1H), 5.40 (q, *J* = 6.6, 14.4 Hz, 1H), 5.61–5.75 (m, 1H), 6.15–6.26 (m, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 38.0, 61.9, 109.9, 118.0, 118.7, 120.0, 123.8, 127.0, 132.4, 132.7, 135.1, 146.1. Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09. Found: C, 72.09; H, 6.97; N, 21.38.

1-[1-(2-Fluorobenzyl)-2-propenyl]-1*H*-1,2,3-benzotriazole (5.2f): Colorless oil; ^{1}H NMR δ 3.58 (d, *J* = 7.8 Hz, 2H), 5.17 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.59 (q, *J* = 7.8, 14.7 Hz, 1H), 6.25–6.36 (m, 1H), 6.82–6.99 (m, 3H), 7.06–7.11 (m, 1H), 7.27–7.43 (m, 3H), 8.01 (d, *J* = 9.3 Hz, 1H); ^{13}C NMR δ 34.3, 61.8, 109.5, 115.1 (d, *J* = 21.7 Hz), 118.4, 119.9, 123.5 (d, *J* = 15.2 Hz), 123.7, 124.0 (d, *J* = 3.3 Hz), 127.0, 128.8 (d, *J* = 8.3 Hz), 131.5 (d, *J* = 4.5 Hz), 132.6, 134.9, 145.8, 161.1 (d, *J* = 243.9 Hz). Anal. Calcd for $C_{16}H_{14}FN_3$: C, 71.89; H, 5.82; N, 15.72. Found: C, 71.67 H, 5.27; N, 15.65.

1-(1-Propyl-2-propenyl)-1*H*-1,2,3-benzotriazole (5.2g): Colorless oil; ^{1}H NMR δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.14–1.36 (m, 2H), 2.09–2.19 (m, 1H), 2.26–2.36 (m, 1H), 5.19 (d, *J* = 17.4 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 5.34–5.41 (m, 1H), 6.12–6.23 (m, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 9.3 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 13.3, 19.0, 35.3, 61.9, 109.9, 117.5, 119.8, 123.6, 126.8, 132.2, 135.7, 146.0. Anal. Calcd for $C_{17}H_{25}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.34; H, 7.86; N, 21.29.

1-(1-Octyl-2-propenyl)-1*H*-1,2,3-benzotriazole (5.2h): Colorless oil; ^{1}H NMR δ 0.84 (t, *J* = 6.9 Hz, 3H), 1.11–1.34 (m, 12H), 2.09–2.19 (m, 1H), 2.21–2.38 (m, 1H), 5.18 (dd, *J* = 0.6, 17.1 Hz, 1H), 5.25 (dd, *J* = 0.6, 10.5 Hz, 1H), 5.31–5.39 (m, 1H), 6.12–6.23 (m, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR δ 13.9, 22.4, 25.8, 28.8, 28.9, 29.1, 31.5, 33.4, 62.3, 109.9, 117.5, 119.8, 123.6, 126.8, 132.2, 135.8, 146.0. Anal. Calcd for $C_{17}H_{25}N_3$: C, 75.23; H, 9.28; N, 15.48. Found: C, 75.32; H, 9.08; N, 15.93.

5.3.2 General Procedure for the Preparation of thioamides 5.4a-g and butenimidothioates 5.9a-g.

1-(1-Alkylprop-2-enyl)-1*H*-benzotriazoles **5.2a-h** (4 mmol) were dissolved in dry THF (30 mL) under argon before the addition of a solution of *n*-BuLi in hexane (1.52 M, 2.6 mL, 4 mmol) at –78 °C. After stirring for 10 min, the isothiocyanate **5.3** (4.1 mmol) was introduced. And the mixtures were stirred for additional 30 min for compounds **5.4a-g** before treatment with saturated aqueous NH_4Cl (30 mL). In the case of **5.9a-j**, after 30 min, methyl iodide (3 equiv) was added and the mixture was allowed to warm to rt overnight before treatment with saturated aqueous NH_4Cl (30 mL). Once separated from the organic layers, the aqueous layers were extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Compounds **5.4a-g** were used in the next step without purification. Compounds **5.9a-j** were purified by pentane : Et_2O (3 :1) on silica gel.

2-(1*H*-Benzotriazol-1-yl)-2-ethyl-*N*-phenylbut-3-enethioamide (5.4a): Recrystallized from Et_2O (0.6 g, 46%). yellow solid; mp 175.3–176.3 °C; ^1H NMR δ 1.09 (t, J = 7.2 Hz, 3H), 2.86–3.07 (m, 2H), 4.61 (d, J = 17.3 Hz, 1H), 5.29 (d, J = 10.8 Hz, 1H), 7.15–7.42 (m, 9H), 7.61 (d, J = 8.3 Hz, 1H), 9.20–10.10 (br s, 1H); ^{13}C NMR δ 8.7, 33.7, 77.7, 112.1, 115.6, 119.1, 124.5, 125.1, 127.4, 127.6, 128.9, 132.2, 137.0, 138.4, 146.0, 199.5.

Methyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-2-ethoxy-*N*-phenyl-3-butenimidothioate (5.9a): White microcrystals; ^1H NMR δ 1.04 (t, J = 6.6 Hz, 3H),2.15 (br s, 3H), 2.50–2.80 (m, 1H), 3.56–3.61 (m, 1H), 5.75 (d, J = 10.7 Hz, 1H), 5.90 (d, J = 17.5 Hz, 1H), 6.00–6.20 (m, 2H), 6.80–7.00 (m, 3H), 7.14 (dd, J = 11.0, 17.6 Hz, 1H), 7.38 (dd, J = 7.4, 7.4 Hz, 1H), 7.53 (dd, J = 7.9, 7.9 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 14.6, 59.3, 111.8, 117.6, 119.6, 119.8, 123.0, 124.2, 127.6, 128.1, 132.0, 132.3, 146.2, 147.9. Anal. Calcd for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.72; N, 15.90. Found: C, 64.42; H, 5.80; N, 15.87.

Methyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-*N*-(4-chlorophenyl)-2-ethoxy-3-butenimidothioate (5.9b): White microcrystals; ^1H NMR δ 1.04 (t, J = 6.8 Hz, 3H), 2.17 (s, 3H), 2.69 (br s, 1H), 3.65–3.51 (m, 1H), 5.76 (d, J = 11.7 Hz, 1H), 5.90 (d, J = 17.4 Hz, 1H), 6.10 (br s, 2H), 6.94 (br s, 2H), 7.12 (dd, J = 11.1, 17.4 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 14.5, 14.9, 59.3, 94.1, 111.6, 118.9, 119.9, 120.0, 124.3, 127.7, 128.0, 131.9, 132.0, 146.2, 146.5, 165.4. Anal. Calcd for $C_{19}H_{19}ClN_4OS$: C, 58.98; H, 4.95; N, 14.48. Found: C, 59.16; H, 5.09; N, 14.48.

Methyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-2-ethoxy-*N*-(4-fluorophenyl)-3-butenimidothioate (5.9c): White microcrystals; ^1H NMR δ 1.05 (br s, 3H), 2.17 (br s, 3H), 2.70 (br s, 1H), 3.59 (br s, 1H), 5.76 (d, *J* = 11.1 Hz, 1H), 5.90 (d, *J* = 17.4 Hz, 1H), 6.60 (br s, 2H), 6.69 (br s, 2H), 7.13 (dd, *J* = 10.8, 17.4 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 14.7(2C), 59.5, 94.0, 111.8, 114.7, 115.0, 119.9, 120.0, 124.3, 127.7, 132.0, 132.2, 144, 146.3, 157.2, 160.5. Anal. Calcd for $C_{19}H_{19}FN_4OS$: C, 61.60; H, 5.17; N, 15.12. Found: C, 61.00; H, 5.29; N, 15.00.

Methyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-2-ethoxy-*N*-(3-fluorophenyl)-3-butenimidothioate (5.9d): White microcrystals; ^1H NMR δ 1.04 (t, *J* = 6.9 Hz, 3H), 2.20 (s. 3H), 2.66 (br s, 1H), 3.68–3.47 (m, 1H), 5.77 (d, *J* = 10.9 Hz, 1H), 5.92 (d, *J* = 17.4 Hz, 1H), 5.46–6.23 (m, 2H), 6.61–6.47 (m, 1H), 7.00–6.82 (m, 1H), 7.16 (dd, *J* = 10.8, 17.4 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 14.6, 14.7, 59.3, 94.1, 104.9 (d, *J* = 23.9 Hz), 109.5 (d, *J* = 21.1 Hz), 111.6, 113.3, 120.0, 120.1, 124.4, 127.8, 129.2 (d, *J* = 9.2 Hz), 132.0, 132.1, 146.3, 149.5 (d, *J* = 9.7 Hz), 162.3 (d, *J* = 130.0 Hz), 165.7. Anal. Calcd for $C_{19}H_{19}FN_4OS$: C, 61.60; H, 5.17; N, 15.12. Found: C, 61.91; H, 5.14; N, 15.15.

Methyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-2-ethoxy-*N*-(4-methoxyphenyl)-3-butenimidothioate (5.9e): White microcrystals; ^1H NMR δ 1.07 (br s, 3H), 2.16 (br s, 3H), 2.83 (br s, 1H), 3.62 (br s, 1H), 3.70 (s, 3H), 5.74 (d, *J* = 11.1 Hz, 1H), 5.87 (d, *J* = 17.4 Hz, 1H), 6.61 (br s, 4H), 7.13 (q, *J* = 10.8, 17.4 Hz. 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 7.51 (t, $J = 7.7$ Hz, 1H), 7.85 (d, $J = 8.4$ Hz, 1H), 8.03 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR δ 14.8, 15.0, 55.3, 59.6, 95.7, 112.0, 113.6, 119.0, 119.6, 119.9, 124.2, 127.6, 132.1, 132.4, 141.2, 146.3, 155.7. Anal. Calcd for $C_{20}H_{22}N_4O_2S$: C, 62.80; H, 5.80; N, 14.65. Found: C, 62.75; H, 6.05; N, 14.62.

Methyl 2-(1*H*-1,2,3-benzotriazol-1-yl)-*N*-(2-chlorophenyl)-2-ethoxy-3-butenimidothioate (5.9g): White microcrystals; ^{1}H NMR δ 1.06 (t. $J = 7.0$ Hz, 3H), 2.11 (s, 3H), 2.88–2.65 (m, 1H), 3.72–3.50 (m, 1H), 5.78 (d, $J = 11.1$ Hz, 1H), 5.87 (d, $J = 17.4$ Hz, 1H), 6.30 (br s, 1H), 6.86 (t, $J = 7.5$ Hz, 1H), 6.97 (t, $J = 7.3$ Hz, 1H), 7.08 (dd, $J = 10.8$, 17.4 Hz, 1H), 7.16 (t, $J = 7.9$ Hz, 1H), 7.39 (t, $J = 8.4$ Hz, 1H), 7.52 (t, $J = 8.1$ Hz, 1H), 7.95 (d, $J = 8.4$ Hz, 1H), 8.05 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR δ 14.6, 14.8, 59.7, 95.0, 112.3, 118.7, 119.9, 120.1, 123.3, 124.1, 124.3, 126.5, 127.7, 129.2, 131.7, 132.1, 145.2, 146.3, 165.7. Anal. Calcd for $C_{19}H_{19}ClN_4OS$: C, 58.98; H, 4.95; N, 14.48. Found: C, 59.16; H, 5.06; N, 14.46.

5.3.3 General Procedure for the Preparation of Thiophenes 5.6a-c,e-g and Pyrrols 5.10a-e,g.

The crude reaction mixtures **5.4a-g** (2 mmol) or pure compounds **5.9a-e** (2 mmol) were dissolved in dry CH_2Cl_2 (30 mL) under argon atmosphere (for **5.9g**, in dry toluene) before the addition of $ZnBr_2$ (1.2 g, 5 mmol). The resulting solutions were allowed to react under reflux for 24 h (for **5.4a-g**, **5.9g**) or 1 h (for **5.9a-f**) until complete conversion of the starting material (TLC control). After addition of aqueous NaOH solution (2 M, 30 mL), the aqueous layers were separated from the organic layers and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixtures were purified by flash column chromatography on silica gel (pentane/Et_2O: 10/1) to afford compounds **5.6a-c,e-g** and **5.10a-e,g** as pure products.

3-Ethyl-*N*-phenyl-2-thiopheneamine (5.6a): Yellow oil; ^{1}H NMR δ 1.13 (t, *J* = 7.4 Hz, 3H), 2.46 (q, *J* = 7.4 Hz, 2H), 5.10 (br s, 1H), 6.64 (d, *J* = 8.2 Hz, 2H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 5.5 Hz, 1H), 6.99 (d, *J* = 5.8 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR δ 14.5, 20.6, 113.6, 118.9, 120.8, 127.0, 129.1, 137.6, 139.0, 147.1. Anal. Calcd for $C_{12}H_{13}NS$: C, 70.89; H, 6.44; N, 6.89. Found: C, 70.51 H, 6.58; N, 7.25.

3-[(2-Chlorophenyl)methyl]-*N*-phenylthiophen-2-amine (5.6b): Colorless oil; ^{1}H NMR δ 3.91 (s, 2H), 5.20 (s, 1H), 6.69–6.74 (m, 3H), 6.80 (t, *J* = 7.1 Hz, 1H), 6.96 (d, *J* = 5.8 Hz, 1H), 7.10–7.20 (m, 5H), 7.30–7.32 (m, 1H); ^{13}C NMR δ 31.2, 114.0, 119.3, 120.7, 126.8, 127.6, 127.7, 129.2, 129.4, 130.5, 133.6, 133.9, 137.9, 139.5, 146.6. Anal. Calcd for $C_{17}H_{14}ClNS$: C, 68.10; H, 4.71; N, 4.67. Found: C, 67.71 H, 4.64; N, 5.04.

3-(2-Chlorobenzyl)-*N*-(3-fluorophenyl)-2-thiophenamine (5.6c): Yellow oil; ^{1}H NMR δ 3.89 (s, 2H), 5.28 (br s, 1H), 6.36 (dt, *J* = 1.5, 11.1 Hz, 1H), 6.43–6.50 (m, 2H), 6.73 (d, *J* = 5.7 Hz, 1H), 6.99 (d, *J* = 5.7 Hz, 1H), 7.00–7.13 (m, 4H), 7.30–7.32 (m, 1H); ^{13}C NMR δ 31.3, 100.8 (d, *J* = 25.3 Hz), 105.7 (d, *J* = 22.1 Hz), 109.6, 121.5, 126.8, 127.7, 127.8, 129.4, 130.2, 130.3, 130.5, 133.8, 134.4, 137.9 (d, *J* = 49.5 Hz), 148.5 (d, *J* = 10.6 Hz), 163.9 (d, *J* = 240.0 Hz). Anal. Calcd for $C_{17}H_{13}ClFNS$: C, 64.25; H, 4.12; N, 4.41. Found: C, 64.11; H, 4.04; N, 4.77.

3-Hexyl-*N*-phenyl-2-thiophenamine (5.6e): Yellow oil; ^{1}H NMR δ 0.84 (t, *J* = 6.6 Hz, 3H), 1.23–1.29 (m, 6H), 1.51–1.55 (m, 2H), 2.46 (t, *J* = 7.8 Hz, 2H), 5.14 (br s, 1H), 6.68 (d, *J* = 7.8 Hz, 2H), 6.78 (t, *J* = 6.9 Hz, 1H), 6.84 (d, *J* = 5.7 Hz, 1H), 7.01 (d, *J* = 5.7 Hz, 1H), 7.18 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR δ 14.1, 22.6, 27.4, 29.1, 30.0, 31.6, 113.7, 119.0, 120.7, 127.4, 129.2, 137.7, 138.0, 147.2. HRMS for $C_{16}H_{22}NS$ [M+1]: 260.1473; Found: 260.1478.

3-Allyl-*N*-(4-chlorophenyl)-2-thiophenamine (5.6f): Yellow oil; ^{1}H NMR δ 3.18 (d, *J* = 6.3 Hz, 2H), 4.96–5.03 (m, 2H), 5.18 (br s, 1H), 5.78–5.92 (m, 1H), 6.58 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 5.4 Hz, 1H), 7.00 (d, *J* = 5.7 Hz, 1H), 7.10 (d, *J* = 9.3 Hz, 2H); ^{13}C NMR δ 31.8, 114.9, 115.7, 120.8, 123.7, 127.7, 129.0, 134.3, 136.0, 138.2, 145.3. Anal. Calcd for $C_{13}H_{12}ClNS$: N, 5.61. Found: N, 6.01.

3-(2-Fluorobenzyl)-*N*-(4-methoxyphenyl)-2-thiophenamine (5.6g): Yellow oil; ^{1}H NMR δ 3.74, (s, 3H), 3.83 (s, 2H), 5.10 (br s, 1H), 6.68–6.80 (m, 5H), 6.91 (d, *J* = 5.7 Hz, 1H), 6.96–7.14 (m, 4H); ^{13}C NMR δ 26.7 (d, *J* = 3.5 Hz), 55.7, 114.7, 115.2 (d, *J* = 22.1 Hz), 115.6, 119.6, 124.0 (d, *J* = 3.5 Hz), 127.3 (d, *J* = 15.5 Hz), 127.7, 127.9 (d, *J* = 8.6 Hz), 130.7 (d, *J* = 4.5 Hz), 132.4, 140.5, 141.0, 153.3, 160.9 (d, *J* = 243.9 Hz). Anal. Calcd for $C_{18}H_{16}FNOS$: N, 4.47. Found: N, 4.61.

3-Ethoxy-2-(methylsulfanyl)-1-phenyl-1*H*-pyrrole (5.10a): Colorless oil; ^{1}H NMR δ 1.42 (t, *J* = 6.9 Hz, 3H), 2.02 (s, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 6.03 (d, *J* = 3.3 Hz, 1H), 6.77 (d, *J* = 3.2 Hz, 1H), 7.31–7.45 (m, 5H); ^{13}C NMR δ 15.1, 20.1, 66.6, 97.3, 107.6, 121.6, 126.0, 126.9, 128.6, 139.7, 151.3. Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.92 H, 6.48; N, 6.00. Found: C, 66.73; H, 6.69; N, 6.35.

1-(4-Chlorophenyl)-3-ethoxy-2-(methylsulfanyl)-1*H*-pyrrole (5.10b): White microcrystals mp 40.0–42.0 °C; ^{1}H NMR δ 1.42 (t, *J* = 6.8 Hz, 3H), 2.02 (s, 3H), 4.10 (q, *J* = 7.2, 13.8 Hz, 2H), 6.04 (d, *J* = 3.0 Hz, 1H), 6.75 (d, *J* = 3.3 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR δ 15.1, 20.2, 66.6, 97.8, 107.6, 121.6, 127.2, 128.8, 132.7, 138.2, 151.6. Anal. Calcd for $C_{13}H_{14}ClNOS$: C, 58.31; H, 5.27; N, 5.23. Found: C, 58.15; H, 5.35; N, 5.15.

Ethyl 1-(4-fluorophenyl)-2-(methylsulfanyl)-1*H*-pyrrol-3-yl ether (5.10c): Colorless oil; ^{1}H NMR δ 1.43 (t, *J* = 7.1 Hz, 3H); 2.02 (s, 3H), 4.11 (q, *J* = 14.1, 6.8 Hz, 2H), 6.03 (d, *J* = 3.6 Hz, 1H), 6.74 (d, *J* = 3.0 Hz, 1H), 7.12 (t, *J* = 8.7 Hz, 2H), 7.41–7.29 (m, 2H); ^{13}C NMR δ 15.2, 20.3, 66.7, 97.5, 115.6 (d, *J* = 22.8 Hz), 121.8, 127.8 (d, *J* = 8.5 Hz), 135.9, 151.3, 161.5 (d, *J* = 240 Hz). Anal. Calcd for $C_{13}H_{14}FNOS$: C, 62.13 H, 5.61; N, 5.57. Found: C, 61.74; H, 5.74; N, 5.89.

Ethyl 1-(3-fluorophenyl)-2-(methylsulfanyl)-1*H*-pyrrol-3-yl ether (5.10d): Light yellow oil; ^{1}H NMR δ 1.42 (t, *J* = 6.6 Hz, 3H), 2.04 (s, 3H), 4.11 (q, *J* = 7.8, 15.0 Hz, 2H), 6.04 (d, *J* = 3.6 Hz, 1H), 6.77 (d, *J* = 4.2 Hz, 1H), 7.08–7.02 (m, 1H), 7.19–7.12 (m, 2H), 7.43–7.30 (m, 1H); ^{13}C NMR δ 15.1, 20.2, 66.6, 97.9, 107.5, 113.3 (d, *J* = 24.1 Hz), 113.7 (d, *J* = 21.1 Hz), 121.5 (d, *J* = 3.0 Hz), 121.7, 129.7 (d, *J* = 9.0 Hz), 141.0 (d, *J* = 10.0 Hz), 151.7, 162.3 (d, *J* = 245.3 Hz). Anal. Calcd for $C_{13}H_{14}FNOS$: C, 62.13 H, 5.61; N, 5.57. Found: C, 61.91; H, 5.70; N, 5.89.

1-(2-Chlorophenyl)-3-ethoxy-2-(methylsulfanyl)-1*H*-pyrrole (5.10e): Yellow microcrystals mp 64.0–66.0 °C; ^{1}H NMR δ 1.35 (t, *J* = 7.1 Hz, 3H), 1.94 (s, 3H), 4.03 (q, *J* = 6.9, 14.1 Hz, 2H), 5.99 (d, *J* = 3.3 Hz, 1H), 6.57 (d, *J* = 3.3 Hz, 1H), 7.34–7.21 (m, 3H), 7.47–7.39 (m, 1H); ^{13}C NMR δ 15.1, 20.1, 66.5, 97.4, 108.3, 122.0, 126.9, 129.4, 129.9, 130.4, 133.0, 137.4, 150.6. Anal. Calcd for $C_{13}H_{14}ClNOS$: C, 58.31; H, 5.27; N, 5.23. Found: C, 58.23; H, 5.47; N, 5.20.

3-Allyl-2-methylsulfanyl-1-phenyl-1*H*-pyrrole (5.10g): Colorless oil; ^{1}H NMR δ 1.95 (s, 3H), 3.43 (d, *J* = 6.6 Hz, 2H), 5.01–5.02 (m, 1H), 5.09–5.16 (m, 1H), 5.95–6.09 (m, 1H), 6.19 (d, *J* = 3.0 Hz, 1H), 6.92 (d, *J* = 2.7 Hz, 1H), 7.34–7.47 (m, 5H); ^{13}C NMR δ 20.6, 31.8, 109.4, 114.7, 120.8, 124.5, 126.4, 127.1, 128.6, 129.6, 138.1, 140.0. Anal. Calcd for $C_{14}H_{15}NS$: C, 73.32 H, 6.59; N, 6.11. Found: C, 72.99; H, 6.68; N, 6.38.

5.3.4 Procedure for the Preparation of *N*-(3-Ethoxythiophen-2-yl)-*N*-substituted amines (5.6d).

Compounds **5.6d** were prepared as derivatives **5.6a-c,e-g** and further methylated as follows before purification. The crude products were dissolved in dry DMF (30 mL) under argon atmosphere before the introduction of sodium hydride (60% in mineral oil, 0.8 g, 20 mmol). The resulting solution was allowed to react for 10 min, before methyliodide (1.25 mL, 20 mmol) was added and the mixture was stirred for 5 h at rt. After addition of water (10 mL), the reaction was extracted with Et_2O (3 × 30 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude reaction mixtures were purified by flash column chromatography on silica gel (pentane/Et_2O: 20/1) to afford compounds **5.6d** as pure products.

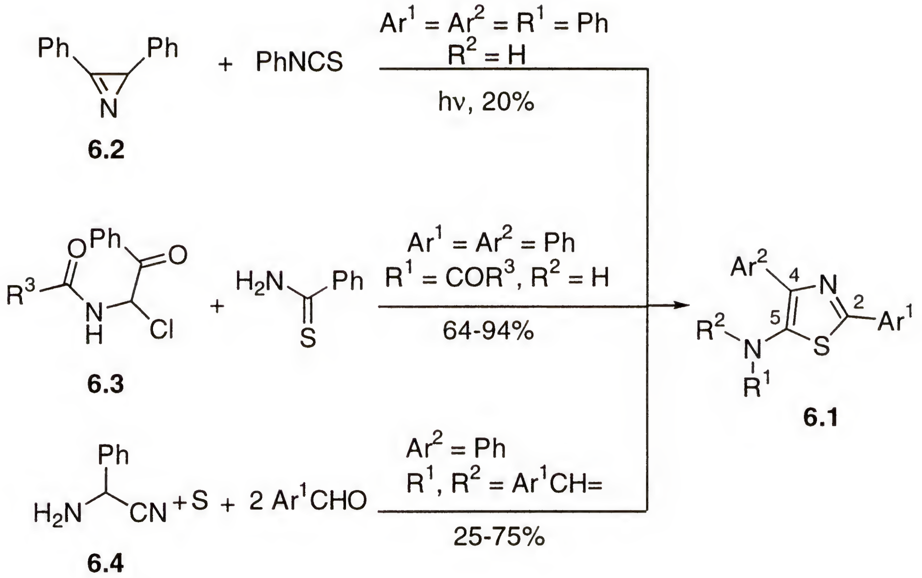
3-(Ethoxy)-*N*-phenylthiophen-2-amine (5.6d): Colorless oil (43% yield); ^1H NMR δ 1.25 (t, *J* = 7.1 Hz, 3H), 3.25 (s, 3H), 4.03 (q, *J* = 7.1 Hz, 2H), 6.76–6.80 (m, 4H), 6.97 (d, *J* = 6.0 Hz, 1H), 7.18–7.25 (m, 2H); ^{13}C NMR δ 15.3, 40.4, 66.8, 113.6, 118.1, 118.3, 128.8, 129.9, 149.1, 150.2. Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.97 H, 6.65; N, 6.30.

CHAPTER 6

[3+2] CYCLOADDITIONS, PART II: A CONVENIENT SYNTHESIS OF 5-AMINO-2,4-DIARYL-*N*-ARYLTHIAZOLES

6.1 Introduction

Thiazoles have found a variety of attractive applications, i.e. as pharmaceuticals [98CPB623, 99CB305, 98MI263, 72USP3704239], dyes and photographic chemicals [79MI154]. For example, simple 2,4-diarylthiazoles such as 2,4-bis(3-indolyl)thiazoles, readily accessible by Hantzsch reactions [1887CB3118], are potent cytotoxic agents [99BMCL569]. Less is known about efficient syntheses of 2,4-diaryl-5-aminothiazoles **6.1**. Literature syntheses (Scheme 6.1) include the following: (i) the photoconversion of unstable azirene **6.2** into thiazole **6.1** (where $Ar^1 = Ar^2 = R^1 = Ph$, $R^2 = H$) in a 20% yield [72HCA916]; (ii) the condensation of unstable ω-chloro-ω-acylamidoacetophenones (**6.3**), with thioformamide furnishing thiazoles **6.1** (where $Ar^1 = Ar^2 = Ph$, $R^1 = COR^3$, $R^2 = H$) in 64–94 % yields [74CH810], which is limited by the need to access of **6.3**, *via* condensation of phenylglyoxal with acid amides and thionyl chloride; (iii) the synthesis of 5-arylidenamino-2-aryl-4-phenylthiazoles in 25–75% yield from aminophenyl-acetonitrile (**6.4**), sulfur and aromatic aldehydes [74JPR299]. However, this method was limited to Ar^2 as phenyl group only and yields were low for the thiazoles bearing electron-withdrawing groups in the 2 position (25%).



Scheme 6.1

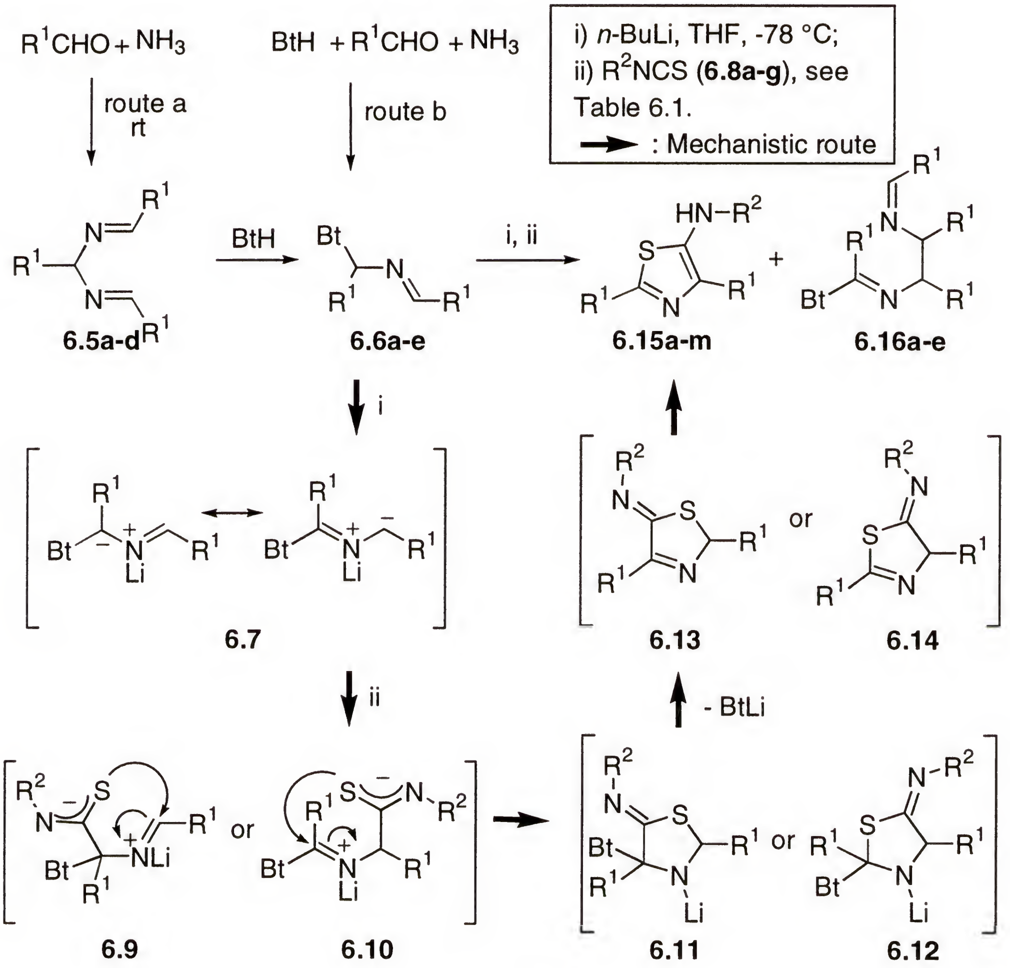
Existing synthetic routes for 5-aminothiazoles [78T611, 84JCS(CC)430, 85CL1115, 88H2177, 91JOC4645, 94JHC877] do not appear to have been used for 2,4-diaryl-5-aminothiazoles. In our group, readily available [91S703] *N*-arylmethylene[(benzotriazol-1-yl)arylmethyl]amines were used in 1,3-dipolar cycloadditions with alkenes or alkynes for the synthesis of pyrroles and dihydropyrroles. [91S863] We now report the use of these building blocks for the convenient synthesis of *N*-substituted-2,4-diaryl-5-aminothiazoles.

6.2 Results and Discussion

N-Arylmethylene[(benzotriazol-1-yl)arylmethyl]amines **6.6a-c,e** (Scheme 6.2) were previously reported [91S703] to be obtained in high yields by stirring a mixture of benzotriazole, the appropriate aromatic aldehyde and ethanolic ammonia at rt (route b).

Compound **6.6e** was indeed prepared cleanly in 90% yield using the published procedure. However, in our hands this method provided the products **6.6a-d** mixed with varying amounts of trimers **6.5a-d.** Therefore we found it more convenient to use a two-step synthesis (Scheme 6.2, route a): intermediate trimers **6.5a-d** were readily obtained in 75–90% yields by stirring the corresponding aldehydes and excess (10 fold) NH_3 solution (or methanolic NH_3 solution) at 20 °C for ca. 10 h [1837LA130, 64JOC1985, 72CJC669]. Subsequent refluxing of **6.5a-d** with benzotriazole in toluene or 1,4-dioxane gave **6.6a-d** in 80–93% yields. This procedure was particularly suitable for compound **6.6c** with an electron-withdrawing group: **6.6c** was obtained in 90% yield. Novel compound **6.6d** functionalized with a thiophene moiety was prepared in 80% yield. Purification on silica gel is not suitable for compounds **6.6a-e** due to the acid-sensitive imine functionality. However, if the imine is solid, recrystallization or removal of excess benzotriazole by washing with saturated Na_2CO_3 solution after reactions, provided the pure imines **6.6a-e**.

Treatment of **6.6a-e** with one equiv of *n*-BuLi in dry THF at –78 °C resulted in a dark solution within seconds, typical of carbanions stabilized by a benzotriazole group [95JOC7612, 98JOC2110]. Presumably the resonance stabilized lithiated azomethine ylide **6.7** (Scheme 6.2) was formed. After 5–10 min, the appropriate isothiocyanate (R^2NCS, **6.8**, 1.1 equiv) was added dropwise while still at –78 °C. The color of the solution changed to dark red ca. 5 min after the complete addition of the electrophile. Any lack of regioselectivity in providing a mixture of intermediates **6.9** and **6.10** is immaterial since isomers **6.9** and **6.10** both cyclize and then aromatize to the same thiazole **6.15**. Consistent with the hypothesis of azomethine ylide **6.7**, is the observation of a precipitate only 15 min after the addition of isothiocyanate at –78 °C. The precipitate was identified by the ^{1}H NMR spectra to be a complex of the benzotriazole lithium salt with THF. The reaction was followed by TLC and found to produce mainly the desired **6.15a-m**. That only thiazoles and no imidazoles were isolated as final products reflects the nucleophilicity of sulfur.



	R^1
6.5a, 6.6a, 6.16a	Ph
6.5b, 6.6b, 6.16b	4-MeC_6H_4
6.5c, 6.6c, 6.16c	4-ClC_6H_4
6.5d, 6.6d, 6.16d	thien-2-yl
6.6e, 6.16e	2,4-$(MeO)_2C_6H_3$

Scheme 6.2

Table 6.1. Synthesis[a] of Thiazole Derivatives **6.15a-m.**

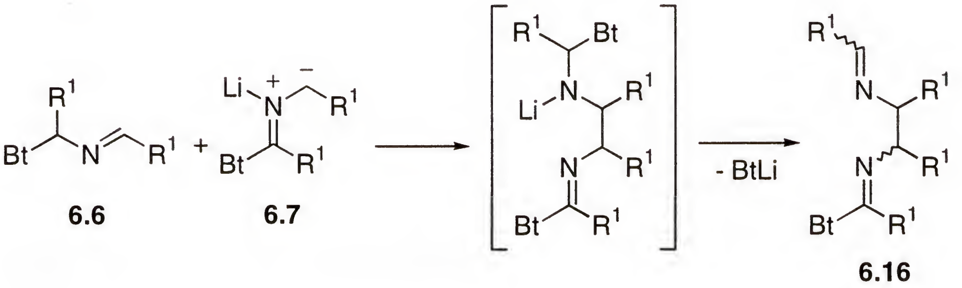
SM	R^1	R^2	Product	Yields (%)[b]
6.6a, 6.8a	Ph	Ph	**6.15a**	81
6.6a, 6.8b	Ph	3-FC_6H_4	**6.15b**	65
6.6a, 6.8c	Ph	4-FC_6H_4	**6.15c**	60
6.6a, 6.8d	Ph	4-ClC_6H_4	**6.15d**	56
6.6a, 6.8e	Ph	2-ClC_6H_4	**6.15e**	35
6.6a, 6.8f	Ph	4-MeC_6H_4	**6.15f**	44
6.6a, 6.8g	Ph	4-MeOC_6H_4	**6.15g**	55
6.6b, 6.8a	4-MeC_6H_4	Ph	**6.15h**	60
6.6c, 6.8a	4-ClC_6H_4	Ph	**6.15i**	61
6.6c, 6.8d	4-ClC_6H_4	4-ClC_6H_4	**6.15j**	80
6.6e, 6.8a	$2,4\text{-(MeO)}_2C_6H_3$	Ph	**6.15k**	55
6.6e, 6.8d	$2,4\text{-(MeO)}_2C_6H_3$	4-ClC_6H_4	**6.15l**	70
6.6d, 6.8a	thien-2-yl	Ph	**6.15m**	47

[a] Compounds **6.6d, 6.15b-e,g,i-l** were made by Mr. Rexiat Maimait. [b] Isolated yield after column chromatography.

Products **6.15a-g** (Table 6.1) were obtained in 35–81% yields as stable solids (except **6.15g** which is an oil) starting from imine **6.6a**. Product **6.15a** was easily obtained in high yield with no substituent on *N*-phenyl ring. Products **6.15b-d** were isolated in reasonable yields of 56–65% after column chromatography starting from electron-deficient phenyl isothiocyanates **6.8b-d**. A lower yield (35%) was observed for **6.15e** starting with 2-chlorophenyl isothiocyanate (**6.8e**) compared with **6.15d** starting with 4-chlorophenyl isothiocyanate (**6.8d,** 56%), possibly due to the steric hindrance of the *ortho*-chloro atom substituted. For the electron-rich isothiocyanates (**6.8f,g**, R^2 = *p*-MeO, *p*-Me), the precipitate took longer to form than in reactions with electron-deficient isothiocyanates, but **6.15f,g** were obtained as expected (44%, 55% yield respectively).

The ^{1}H NMR spectra of **6.15a-g** all show signals from phenyl rings directly attached to the thiazole ring appearing between 7.2–8.0 ppm. Proton signals from the *N*-phenyl rings occur between 6.7–7.3 ppm. The NH-proton signals typically show around 5.5 ppm (for **6.15a-d,f,g**), except that for **6.15e** which is shifted downfield to 6.1 ppm, perhaps by a steric effect.

The formation of the by-products **6.16** can be explained by the self-condensation mechanism depicted in Scheme 6.3. This mechanistic proposal is supported by the fact that **6.16a** (R^1 = Ph) could be obtained in 50 % yield as a single isomer (which isomerized during column chromatography on silica gel) by reacting **6.6a** (2 equiv) with BuLi (1 equiv).



Scheme 6.3

The reaction of **6.6b** with phenyl isothiocyanate (**6.8a**) gave the expected thiazole **6.15h** (60%) as yellow needles. The typical ^{1}H NMR peak for the proton on nitrogen occurs at 5.5 ppm. Thus, the methyl substituents on the two phenyl rings make little difference to the NMR shift of the NH-proton. Self-condensation of **6.6b** was observed as a minor side reaction (<10%).

When there was an electron-withdrawing group such as chlorine in **6.6c**, the reaction went smoothly with both phenyl (**6.8a**) and 4-chlorophenyl isothiocyanate (**6.8d**). The fact that the self-condensation products were hardly observed from the ^{1}H

NMR spectra of crude mixtures is consistent with the relatively stable carbanion **6.7**. The ^{1}H NMR signal for the proton on nitrogen appeared at 5.5 ppm for **6.15i** and 5.6 ppm for **6.15j**.

Products with strong electron-donating moieties, like methoxy groups in **6.15k** and **6.15l**, were obtained in 55% and 70% yields respectively. There are significant shifts in the ^{1}H NMR spectra for the protons of the phenyl ring directly attached to the thiazole ring compared with ones for **6.15a-j**. The protons on these phenyl rings show signals in the range 6.9–8.3 ppm. The peak for the proton attached to the nitrogen shifts downfield to 6.4–6.5 ppm. In the ^{1}H NMR spectra of crude mixtures, there were no peaks at 4.00–6.00 ppm for the suggested self-condensation product, possibly, these peaks were also shifted downfield because of the strong electron-donating moieties in the molecule.

1*H*-1,2,3-Benzotriazol-1-yl(2-thienyl)-*N*-[(*E*)-2-thienylmethylidene]methanamine (**6.6d**) was successfully deprotonated and further reacted with phenyl isothiocyanate **6.8a** to result in the final product **6.15m** in reasonable yield. During work-up, brine solution was used instead, as 2 M NaOH solution decomposed **6.15m** significantly. A minor self-condensation product observed from the ^{1}H NMR spectrum of the crude product was represented by two doublet-doublet peaks at 5.28 and 5.53 ppm.

In conclusion, we have developed a practical and facile way to synthesize 2,4-diaryl-*N*-substituted-5-aminothiazoles in moderate to good yields. In contrast to the literature procedures, our methodology allows a simple and straightforward access to the desired target compounds **6.15** only requiring stable and easily available starting materials.

6.3 Experimental Section

Melting points were determined with a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer and uncorrected. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or $CDCl_3$ as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel (230–400 mesh).

6.3.1 General Procedure for the Synthesis of Compounds 6.5a-d.

Aldehydes (0.1 mol) were added to aqueous NH_3 (1 mol, 30%) or methanolic NH_3 (for **6.5d**, 38 mL) and stirred vigorously for 10 h (or until precipitates formed) at rt. The crude products were filtered, washed with water and recrystallized from ethanol to give pure products **6.5a-d**.

Phenyl-*N*,*N*-bis[(*E*)-phenylmethylidene]methanediamine (6.5a): White solid (yield 95%); mp 99.0–99.9 °C (lit. [06M839] mp 102 °C).

(4-Methylphenyl)-*N*,*N*-bis[(*E*)-(4-methylphenyl)methylidene]methanediamine (6.5b): White solid (yield 80%); mp 89.3–90.5 °C (lit. [06M839] mp 91 °C).

(4-Chlorophenyl)-*N*,*N*-bis[(*E*)-(4-chlorophenyl)methylidene]methanediamine (6.5c): White microcrystals (yield 85%); mp 87.8–88.7 °C (lit. [64JOC1985] mp 87–90 °C).

2-Thienyl-*N*,*N*-bis[(*E*)-2-thienylmethylidene]methanediamine (6.5d): Pale brown microcrystals (yield 75%); mp 111.0–111.8 °C (lit. [11CZ1852] mp 111.5 °C).

6.3.2 General Procedure for the Synthesis of Compounds 6.6a-d. Pure compounds **6.5a-d.**

(20mmol) and benzotriazole (37 mmol, 1.5 equiv) were dissolved in 1,4-dioxane (for **6.6a**) or toluene (for **6.6b-d**) (100 mL) and refluxed for 12 h. The reaction mixture was cooled to rt and the solvent was removed. The crude mixture was recrystallized (by ethyl acetate/hexanes), to give pure product **6.6a,d.** Otherwise, the crude mixture was dissolved in ether and washed with saturated K_2CO_3 to remove excess BtH. The organic layer was dried over $MgSO_4$. Upon removal of the $MgSO_4$ and solvent, oily products **6.6b,c** were obtained and can be used further without any purification.

1*H*-1,2,3-Benzotriazol-1-yl(phenyl)-*N*-[(*E*)-phenylmethylidene]methanamine (6.6a): White powder (yield 92%); mp 115.9–118.4 °C (lit. [91S703] 129–130 °C); ^{1}H NMR δ 7.31–7.52 (m, 11H), 7.58 (s, 1H), 7.85 (dd, *J* = 1.8, 8.1 Hz, 2H), 8.05–8.08 (m, 1H), 8.38 (s, 1H); ^{13}C NMR δ 83.8, 112.1, 119.8, 124.0, 126.9, 127.3, 128.7, 128.8, 128.9, 129.0, 131.8, 132.0, 134.8, 137.6, 146.7, 164.0.

1*H*-1,2,3-Benzotriazol-1-yl(4-methylphenyl)-*N*-[(*E*)-(4-methylphenyl)methylidene]methanamine (6.6b): Yellow oil (yield 93%); ^{1}H NMR δ 2.32(s, 3H), 2.38 (s, 3H), 5.27 (s, 1H), 7.14–7.24 (m, 4H), 7.29–7.37 (m, 4H), 7.46–7.51 (m, 2H), 7.72 (d, *J* = 7.8 Hz, 2H), 8.05–8.28 (m, 1H), 8.32 (s, 1H); ^{13}C NMR δ 21.1, 21.6, 83.8, 112.2, 119.8, 123.9, 126.8, 127.2, 128.9, 129.4, 129.5, 131.9, 132.4, 134.9, 138.7, 142.4, 146.8, 163.7.

1*H*-1,2,3-Benzotriazol-1-yl(4-chlorophenyl)-*N*-[(*E*)-(4-chorophenyl)methylidene]methanamine (6.6c): Yellow oil (yield 90%); ^{1}H NMR δ 7.25–7.43 (m, 9H), 7.53 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 8.04–8.08 (m, 1H), 8.29 (s, 1H); ^{13}C NMR δ 82.7, 111.6, 119.9, 124.2, 127.6, 128.2, 129.0, 129.1, 130.1, 131.6, 133.0, 134.9, 135.8, 138.2, 146.7, 163.0.

1*H*-1,2,3-Benzotriazol-1-yl(2-thienyl)-*N*-[(*E*)-2-thienylmethylidene]methanamine (6.6d): Brown powder (yield 80%); mp 101.0–102.2 °C; ^{1}H NMR δ 6.90–7.10 (m, 1H), 7.05–7.10 (m, 2H), 7.30–7.39 (m, 4H), 7.50–7.52 (m, 2H), 7.75 (s, 1H), 8.04–8.07 (m, 1H), 8.37 (s, 1H); ^{13}C NMR δ 79.6, 112.1, 119.8, 124.1, 126.2, 126.6, 127.2, 127.5, 127.8, 131.3, 131.5, 133.3, 140.7, 140.8, 146.7, 156.9. Anal. Calcd for $C_{16}H_{12}N_4S_2$: C, 59.23; H, 3.73; N, 17.27. Found: C, 59.26; H, 3.72; N, 17.17.

6.3.3 Procedure for the Synthesis of 1*H*-1,2,3-Benzotriazol-1-yl(2,4-dimethoxyphenyl)-*N*-[(*E*)-(2,4-dimethoxyphenyl)methylidene]methanamine (6.6e).

2,4-Dimethoxybenzaldehyde (5 g, 30 mmol) was dissolved in 18 mL absolute ethanol, followed by the addition of benzotriazole (7.6 g, 75 mmol) and methanolic ammonia (17 mL, 75 mmol) and stirred overnight at rt. White precipitate was sucked off and washed with ethanol to give white powder as **6.6e** in 90% yield. mp 161.6–163.2 °C (lit. [91S703] 166–167 °C); ^{1}H NMR δ 3.63 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 6.40 (d, J = 5.4 Hz, 2H), 6.52 (t, J = 9.9 Hz, 2H), 7.26–7.32 (m, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 8.00–8.08 (m, 2H), 8.76 (s, 1H); ^{13}C NMR δ 55.3, 55.4, 79.2, 97.8, 98.5, 104.1, 105.6, 111.7, 117.0, 118.9, 119.6, 123.4, 126.7, 129.1, 129.4, 132.4, 146.3, 158.1, 158.7, 160.8, 161.4, 163.9.

6.3.4 General Procedure for the Synthesis of Compounds 6.15a-m.

n-BuLi (1.6 M, 2.5 mL, 4 mmol) was added to a solution of the corresponding *N*-arylmethylene[(benzotriazole-1-yl)arylmethyl]amines **6.6** (4 mmol) in THF (50 mL) at –78 °C under argon. After stirring for 5 min, isothiocyanate (4.1 mmol) **6.8** was added. If precipitates were observed after around 15 min and TLC showed the desired product, the reaction mixture was quenched at –78 °C by an aqueous NaOH solution (2 M, 30 mL).

Otherwise the reaction mixture was allowed to warm to rt overnight, before being washed with an aqueous NaOH (2 M, 30 mL) or brine (saturated, 30 mL) solution. After separation, the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue were purified by flash chromatography using pentane/ethyl ether mixtures as the eluent.

***N*,2,4-Triphenyl-1,3-thiazol-5-amine (6.15a):**Yellow microcrystals (yield 81%); mp 125.0–125.7 °C (lit. [72HCA916] mp 122.5–124.0 °C); ^{1}H NMR δ 5.48 (br s, 1H), 6.84–6.91 (m, 3H), 7.19–7.39 (m, 8H), 7.92–7.94 (m, 4H); ^{13}C NMR δ 114.8, 120.4, 126.1, 127.7, 127.8, 128.6, 128.8, 129.5, 129.7, 133.9, 134.0, 135.6, 145.3, 146.7, 160.6. Anal. Calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 77.09; H, 5.03; N, 8.61.

Phenyl-*N*,*N*-bis[(*E*)-phenylmethylidene]methanediamine (6.15b): Yellow microcrystals (yield 65%); mp 119.7–120.2 °C; ^{1}H NMR δ 5.57 (s, 1H), 6.56–6.65 (m, 3H), 7.17–7.32 (m, 1H), 7.34–7.46 (m, 1H), 7.91–7.97 (m, 4H); ^{13}C NMR δ 101.7 (d, J = 25.6 Hz), 106.9 (d, J = 21.0 Hz), 110.2 (d, J = 2.5 Hz), 127.8, 128.1, 128.6, 128.9, 130.0, 130.7 (d, J = 10.1 Hz), 133.7, 133.8, 134.1, 147.3 (d, J = 10.1 Hz), 147.9, 161.9, 162.9 (d, J = 243.3 Hz). Anal. Calcd for $C_{21}H_{15}FN_2S$: C, 72.81; H, 4.36; N, 8.09. Found: C, 72.46; H, 4.33; N, 8.03.

***N*-(4-Fluorophenyl)-2,4-diphenyl-1,3-thiazol-5-amine (6.15c):** Yellow microcrystals (yield 60%); mp 109.5–110.5 °C; ^{1}H NMR δ 5.50 (s, 1H), 6.84–6.88 (m, 2H), 6.94–7.00 (m, 2H), 7.31–7.38 (m, 1H), 7.41–7.44 (m, 5H), 7.93–7.96 (m, 4H); ^{13}C NMR δ 116.1, 116.2 (d, J = 22.2 Hz), 126.1, 127.7, 127.9, 128.7, 128.9, 129.8, 133.9, 134.0, 136.1, 141.6, 146.5, 155.9, 159.8 (d, *J* = 102.5 Hz). Anal. Calcd for $C_{21}H_{15}FN_2S$: C, 72.81; H, 4.36; N, 8.09. Found: C, 72.87; H, 4.53; N, 8.03.

***N*-(4-Chlorophenyl)-2,4-diphenyl-1,3-thiazol-5-amine (6.15d):** Yellow microcrystals (yield 56%); mp 128.0–129.3 °C; ^1H NMR δ 5.50 (s, 1H), 6.78 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.23–7.42 (m, 6H), 7.90–7.95 (m, 4H); ^{13}C NMR δ 115.8, 125.2, 126.2, 127.8, 128.0, 128.6, 128.9, 129.4, 130.0, 133.8, 134.8, 144.0, 147.5, 161.4. Anal. Calcd for $C_{21}H_{15}ClN_2S$: C, 69.51; H, 4.17; N, 7.72. Found: C, 69.32; H, 4.22; N, 7.69.

***N*-(2-Chlorophenyl)-2,4-diphenyl-1,3-thiazol-5-amine (6.15e):** Yellow microcrystals (yield 35%); mp 108.1–109.5 °C ; ^1H NMR δ 6.11 (s, 1H), 6.81 (dt, *J* = 8.1, 1.5 Hz, 1H), 6.96 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.13 (td, *J* = 8.4, 1.2 Hz, 1H), 7.31–7.46 (m, 7H), 7.95–7.99 (m, 4H); ^{13}C NMR δ 114.2, 120.0, 120.5, 126.3, 127.7, 128.0, 128.1, 128.6, 128.9, 129.4, 130.0, 133.5, 133.7, 133.9, 141.7, 148.5, 162.2. Anal. Calcd for $C_{21}H_{15}ClN_2S$: C, 69.51; H, 4.17; N, 7.72. Found: C, 69.63; H, 4.23; N, 7.67.

***N*-(4-Methylphenyl)-2,4-diphenyl-1,3-thiazol-5-amine (6.15f):** Yellow microcrystals (yield 44%); mp 101.1–103.0 °C; ^1H NMR δ 2.29 (s, 3H), 5.51 (s, 1H), 6.85 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 7.30–7.38 (m, 1H), 7.38–7.42 (m, 5H), 7.92–7.96 (m, 4H); ^{13}C NMR δ 20.6, 115.2, 126.1, 127.6, 127.7, 128.6, 128.8, 129.7, 130.0, 130.2, 134.0, 134.2, 136.6, 142.8, 145.7, 159.8. Anal. Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 76.83; H, 5.47; N, 8.13.

***N*-(4-Methoxyphenyl)-2,4-diphenyl-1,3-thiazol-5-amine (6.15g):** Thick oil (yield 55%); ^1H NMR δ 3.71 (s, 3H), 5.47 (s, H), 6.81 (q, *J* = 9.0, 15.3 Hz, 4H), 7.23–7.38 (m, 6H), 7.88–7.94 (m, 4H); ^{13}C NMR δ 55.5, 114.8, 117.0, 125.9, 127.5, 127.6, 128.5, 128.7, 129.5, 134.0, 134.2, 138.1, 138.8, 144.5, 154.3, 158.8. Anal. Calcd for $C_{22}H_{18}N_2OS$: C, 73.71; H, 5.06; N, 7.81. Found: C, 73.26; H, 5.51; N, 7.79.

***N*-[2,4-Bis(4-methylphenyl)-1,3-thiazol-5-yl]-*N*-phenylamine (6.15h):** Yellow needles (yield 60%); mp 143.2–143.3 °C; ^{1}H NMR δ 2.34 (s, 3H), 2.37 (s, 3H), 5.45 (s, 1H), 6.86–6.90 (m, 3H), 7.17–7.27(m, 6H), 7.81–7.85 (m, 4H); ^{13}C NMR δ 21.3, 21.4, 114.6, 120.2, 126.0, 127.7, 129.2, 129.5, 131.3, 131.4, 134.4, 137.6, 139.9, 145.5, 147.0, 161.1. Anal. Calcd for $C_{23}H_{20}N_2S$: C, 77.49; H, 5.65; N, 7.86. Found: C, 77.43; H, 5.71; N, 7.84.

2,4-Bis(4-chlorophenyl)-*N*-phenyl-1,3-thiazol-5-amine (6.15i): Yellow microcrystals (yield 61%); mp 44.5–45.5 °C; ^{1}H NMR δ 5.50 (s, 1H), 6.86–6.96 (m, 3H), 7.24–7.29 (m, 2H), 7.32–7.41 (m, 4H), 7.83–7.93 (m, 4H); ^{13}C NMR δ 114.9, 120.9, 127.3, 128.8, 129.0, 129.1, 129.6, 132.3, 133.7, 135.9, 136.3, 144.9, 145.8, 159.6. Anal. Calcd for $C_{21}H_{14}Cl_2N_2S$: C, 63.48; H, 3.55; N, 7.05. Found: C, 63.31; H, 3.65; N, 6.84.

***N*,2,4-Tris(4-chlorophenyl)-1,3-thiazol-5-amine (6.15j):** Yellow microcrystals (yield 80%); mp 73.4–74.6 °C; ^{1}H NMR δ 5.54 (s, 1H), 6.73 (d, J = 9.0 Hz, 2H), 7.16–7.19 (m, 2H), 7.23–7.38 (m, 4H), 7.82 (t, J = 7.8 Hz, 4H); ^{13}C NMR δ 115.8, 125.5, 127.2, 128.7, 128.9, 129.1, 129.4, 131.9, 132.0, 133.7, 135.4, 136.0, 143.6, 146.3, 160.2. Anal. Calcd for $C_{21}H_{13}Cl_3N_2S$: C, 58.42; H, 3.03; N, 6.49. Found: C, 58.60; H, 3.15; N, 6.51.

2,4-Bis(2,4-dimethoxyphenyl)-*N*-phenyl-1,3-thiazol-5-amine (6.15k): Yellow microcrystals (yield 55%); mp 141.7–144.3 °C; ^{1}H NMR δ 3.81 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 6.48–6.64 (m, 5H), 6.80 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.5 Hz, 2H), 7.63 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H); ^{13}C

NMR δ 55.3, 55.4, 55.5, 56.1, 98.2, 99.3, 105.5, 105.9, 114.7, 116.3, 117.1, 119.6, 128.8, 129.1, 132.3, 136.6, 139.2, 145.2, 152.4, 156.9, 157.0, 160.7, 161.3. Anal. Calcd for $C_{25}H_{24}N_2O_4S$: C, 66.94; H, 5.39; N, 6.25. Found: C, 66.56; H, 5.21; N, 6.16.

2,4-Bis(2,4-dimethoxyphenyl)-*N*-(4-chloro)phenyl-1,3-thiazol-5-amine (6.15l): Yellow microcrystals (yield 70%); mp 151.5–153.0 °C; ^{1}H NMR δ 3.83 (s, 6H), 3.84 (s, 3H), 3.85 (s, 3H), 6.43 (s, 1H), 6.52–6.65 (m, 4H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.13 (d, *J* = 9.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 8.32 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ 55.4, 55.5, 55.6, 56.3, 98.3, 99.4, 105.6, 105.9, 115.9, 116.2, 117.0, 124.1, 128.9, 129.0, 132.3, 135.9, 139.9, 144.0, 153.1, 156.9, 157.1, 160.8, 161.5. Anal. Calcd for $C_{25}H_{23}ClN_2O_4S$: C, 62.17; H, 4.80; N, 5.80. Found: C, 62.39; H, 5.02; N, 5.81.

***N*-Phenyl-2,4-di(2-thienyl)-1,3-thiazol-5-amine (6.15m):** Yellow microcrystals (yield 47%); mp 141.1–143.1 °C; ^{1}H NMR δ 5.39 (s, 1H), 6.83–6.88 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 7.01–7.06 (m, 2H), 7.22–7.27 (m, 3H), 7.37–7.42 (m, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.60 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR δ 114.7, 120.6, 125.7, 125.8, 126.4, 127.3, 127.8, 129.5, 132.3, 136.1, 137.7, 143.0, 144.9, 156.0. Anal. Calcd for $C_{17}H_{12}N_2S_3$: C, 59.97; H, 3.55; N, 8.23. Found: C, 59.94; H, 3.64; N, 8.12.

6.3.5 The Preparation of *N*-[1*H*-1,2,3-Benzotriazol-1-yl(phenyl)methylidene]-*N*-[phenylmethylidene]-1,2-(1,2-diphenyl)ethanediamine (6.16a).

The imine **6.6a** (1.24 g, 4 mmol) was dissolved in dry THF (40 mL) under argon, followed by the addition of *n*-BuLi (1.4 mL, 2 mmol) at –78 °C. The mixture was left for 12 h to warm up to rt gradually and saturated NH_4Cl solution (30 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (20 mL × 2). The organic layers were combined and dried over Na_2SO_4 for 6 h. Removal of the drying reagent and solvent gave a crude mixture 1.14 g as a yellow foamy powder. The crude mixture was then purified by column chromatography on silica-gel with Et_2O : pentane (1 : 1). Pure products which are yellow powder were obtained as isomers (0.5 g, 50%). mp 216.0–224.7 °C; ^1H NMR δ 5.07 (d, $J = 6.6$ Hz, 1H), [5.10 (d, $J = 6.0$ Hz, 1H)], 5.17 (d, $J = 6.6$ Hz, 1H), [5.43 (d, $J = 6.0$ Hz, 1H)], 6.43 (d, $J = 8.1$ Hz, 1H), 6.81–7.77 (m, 23H), [6.81–7.77 (m, 25H)], 7.99 (d, $J = 8.4$ Hz, 1H). Anal. Calcd for $C_{34}H_{27}N_5$: C, 80.77; H, 5.38; N, 13.85. Found: C, 80.62; H, 5.46; N, 13.65.

CHAPTER 7
CONCLUSION

N-Substituted benzotriazoles $BtCH_2R$ or $BtCHR^1R$ (R = aryl, vinyl, etc) are powerful synthetic building blocks. They are easily functionalized by deprotonation and alkylation of the resulting carbanions with electrophiles or by substitution of the benzotriazole moiety with nucleophiles. Hence, *N*-substituted benzotriazoles can be regarded as synthetic equivalents for so-called 1,1-dipole synthons (Figure 7.1).

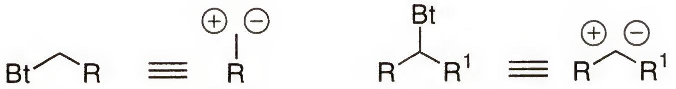
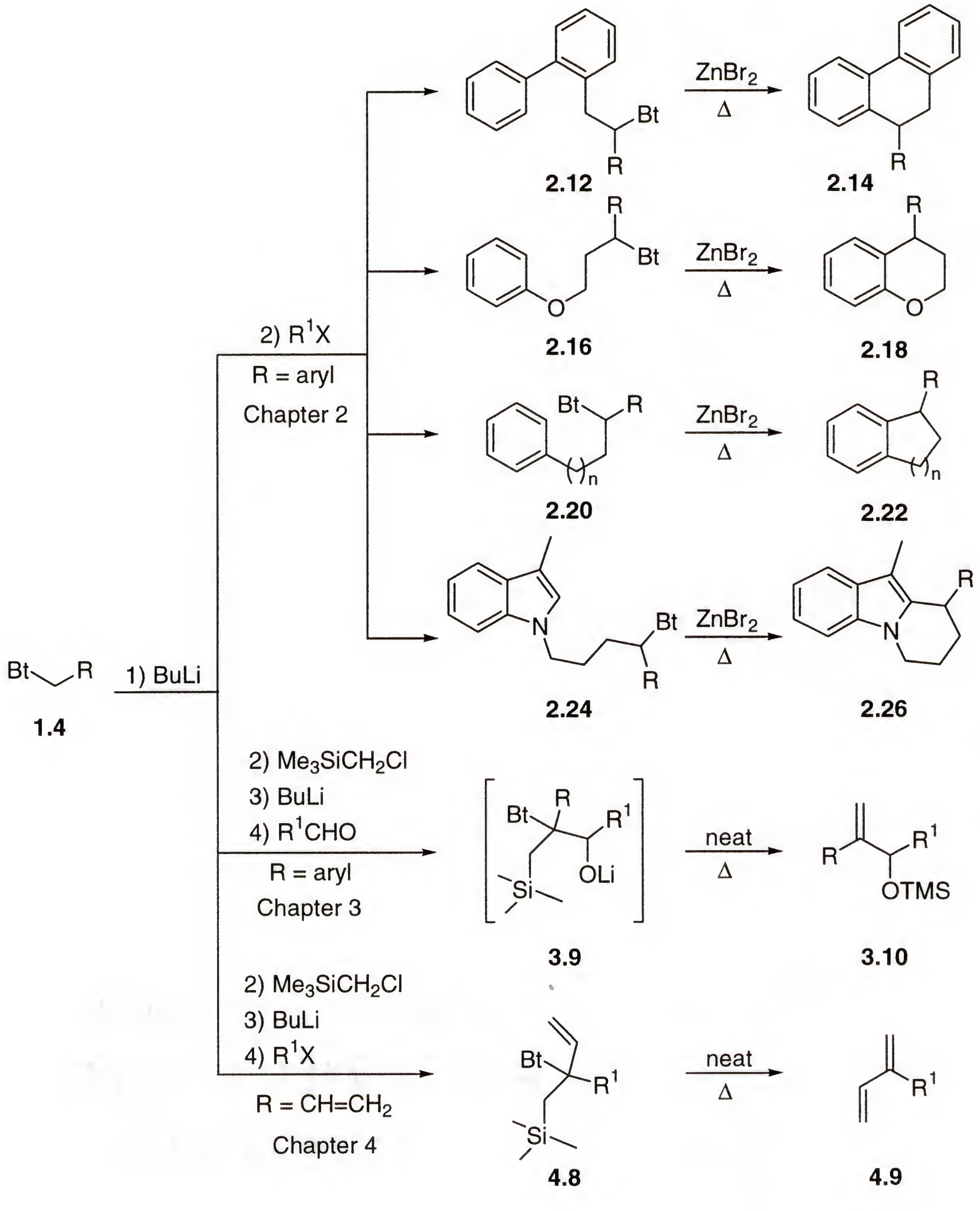


Figure 7.1

Among other things, the high value and the extreme versatility of *N*-substituted benzotriazoles **1.4** as 1,1-dipole synthons were demonstrated by deprotonation / alkylation reaction sequences furnishing the stable intermediates **2.12**, **2.16**, **2.20**, **2.24**, **3.9**, and **4.8** in generally high yields (Scheme 7.1). They were used successfully for the synthesis of carbocyclic or heterocyclic compounds such as **2.14**, **2.18**, **2.22**, or **2.26** by $ZnBr_2$-mediated intramolecular alkylation of aromatic compounds under the substitution of the benzotriazole moiety, or for the synthesis of *O*-trimethylsilyl allylic alcohols **3.10** by [1,4]-C→O silicon migration and concerted elimination of benzotriazole, or for the synthesis of 2-substituted butadienes **4.10** by elimination of $Bt\text{-}SiMe_3$ (Scheme 7.1).



Scheme 7.1

Special 1,1-dipole synthons like *N*-allyl benzotriazole or **6.6** can also be used as synthetic equivalents for the 1,3-dipoles depicted in Figure 7.2.

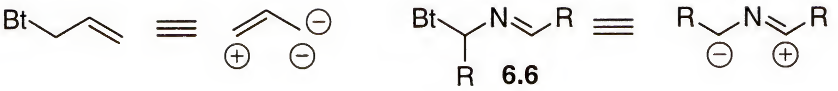
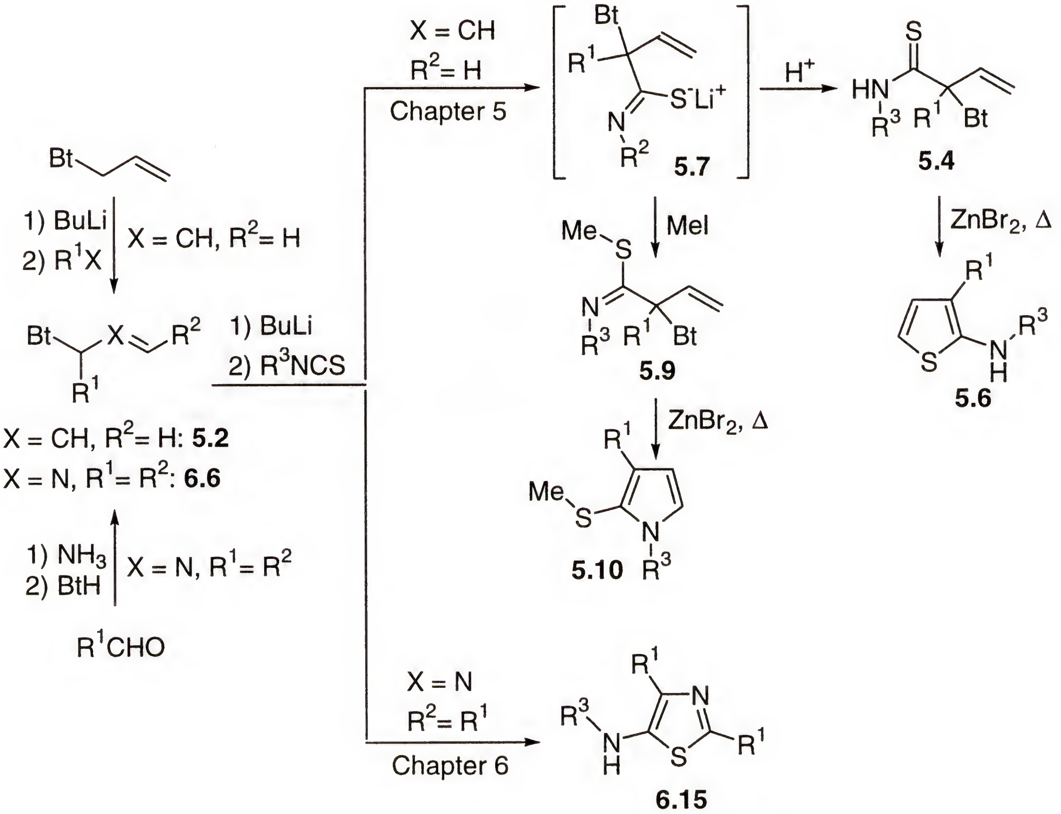


Figure 7.2

Thus, the application of these compounds in formal [3+2] cycloaddition reactions was investigated providing substituted thiophenes **5.6**, pyrroles **5.10** and thiazoles **6.15** in generally good yields (Scheme 7.2).



Scheme 7.2

In summary, benzotriazole derived synthetic equivalents for 1,1-dipole synthons are easily accessible from inexpensive starting materials. Their use provides highly convenient, versatile and efficient routes to a great variety of valuable target compounds usually difficult to obtain (if at all) by alternative methods and should be widely applicable in organic synthesis. However, the potential of this methodology is definitely not exhausted yet.

LIST OF REFERENCES

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Some commonly used additional notes are given below:

1. The list of reference is arranged in the order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
2. In the reference list, the code is followed by the complete literature citation in the ACS style.
3. For journals which are published in separate parts, the part letter of number is given (when necessary) in parentheses immediately after the journal code letter.
4. Journal column numbers are not included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parenthesis immediately after the journal code letters.
5. Patents are assigned appropriate three letter codes.
6. Frequently cited books are assigned codes, but the whole code is now prefixed by the letter "B-".

7. Less common journals and books are given the code "MI" for miscellaneous.

8. Where journals have changed names, the same code is used throughout.

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BIOGRAPHICAL SKETCH

Xiaojing Wang was born in January, 1973, in Dalian Province, P. R. China. She received a B.S. degree in chemistry from Peking University in July, 1996.

She started the Ph.D. program in the Chemistry Department of the University of Florida in August, 1996, under the supervision of Professor Katritzky.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

Alan R. Katritzky, Chair
Kenan Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

William R. Dolbier, Jr.
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

John Reynolds
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

Weihong Tan
Assistant Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

Nicholas Bodor
Graduate Research Professor of
Pharmaceutics

This thesis was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Dean, Graduate School